



(19) Eur päisch s Patentamt  
Europ an Pat nt Office  
Office ur pé n d br vets



(11) EP 0 703 221 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:  
27.03.1996 Bulletin 1996/13

(51) Int Cl.<sup>6</sup>: C07D 221/10, C07D 401/12,  
C07D 413/12, C07D 417/12,  
A61K 31/435

(21) Application number: 95306551.3

(22) Date of filing: 18.09.1995

(84) Designated Contracting States:  
AT BE CH DE DK ES FR GB GR IE IT LI LU NL  
PT SE

(30) Priority: 20.09.1994 US 309282

(71) Applicant: ELI LILLY AND COMPANY  
Indianapolis, Indiana 46285 (US)

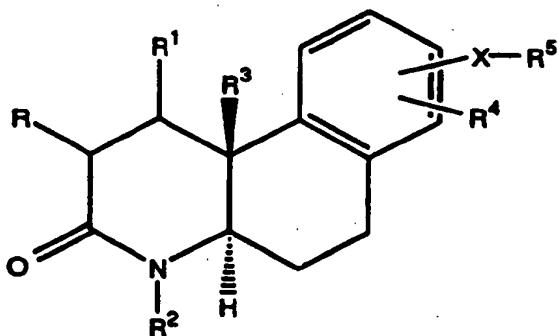
(72) Inventors:  
• Audia, James Edmund  
Indianapolis, Indiana 46278 (US)  
• Haehl, Kevin Lee  
Greenwood, Indiana 46142 (US)

- Kress, Thomas Joseph  
Greenwood, Indiana 46143 (US)
- McQuaid, Loretta Ames  
Indianapolis, Indiana 46254 (US)
- Neubauer, Blake Lee  
Indianapolis, Indiana 46220 (US)
- Rocco, Vincent Patrick  
Indianapolis, Indiana 46208 (US)
- Wepsiec, James Patrick  
Indianapolis, Indiana 46254 (US)

(74) Representative: Hudson, Christopher Mark et al  
Lilly Industries Limited  
European Patent Operations  
Erl Wood Manor  
Windlesham Surrey GU20 6PH (GB)

(54) 5 alpha-reductase Inhibitors

(57) A series of benzoquinolin-3-ones are pharmaceuticals effective in treating conditions consequent on both Type I and Type II 5 $\alpha$ -reductase. The compounds have the formula



I

wherein

R and R<sup>1</sup> both represent hydrogen or combine to form a bond;

R<sup>2</sup> represents hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sup>3</sup> represents methyl or ethyl;

R<sup>4</sup> and -X-R<sup>5</sup> each occupies one of the 7-, 8-and 9-positions;

R<sup>4</sup> represents hydrogen, halo, methyl or ethyl;

X represents C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, a bond, -SO-, -SO<sub>2</sub>-, -CO-Y-(CH<sub>2</sub>)<sub>n</sub>-, -Y-CO-(CH<sub>2</sub>)<sub>n</sub>-, -CO-, -Z-(CH<sub>2</sub>)<sub>n</sub>-, or -SO<sub>3</sub>-, wherein X groups which are not symmetrical may be in either orientation;

Y represents -S-, -O-, or -NH-;

Z represents -O- or -S-;

n represents 0-3;

R<sup>5</sup> represents phenyl, naphthalenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, anthracenyl, acenaphthalenyl, thiazolyl, benzimidazolyl, indazolyl, thiophenyl, phenanthrenyl, quinolinyl, fluorenlyl, isoquinolinyl, indanyl, benzopyranyl, indolyl, benzisoquinolinyl, benzindolyl, benzothiazolyl, benzothiophenyl, quinoxalinyl, benzoxazolyl, tetrazolyl, naphtho-

thiazolyl, quinazolinyl, thiazolopyridinyl, pyridazinoquinazolinyl, benzisothiazolyl, benzodioxolyl, benzodioxinyl, diphenylmethyl or triphenylmethyl;

the above R<sup>5</sup> groups are unsubstituted or substituted with 1-3 groups chosen from the group consisting of halo, trifluoromethyl, trifluoroethoxy, C<sub>1</sub>-C<sub>4</sub> alkyl, trifluoromethoxy, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, nitro, C<sub>1</sub>-C<sub>3</sub> alkylthio, C<sub>1</sub>-C<sub>6</sub> alkanoyl, phenyl, oxo, phenoxy, phenylthio, C<sub>1</sub>-C<sub>3</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, cyano, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, diphenylmethylamino, triphenylmethylamino, benzyloxy, benzylthio, (mono-halo, nitro or CF<sub>3</sub>)benzyl(oxy or thio), di(C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or C<sub>4</sub>-C<sub>6</sub> cycloalkylalkyl)amino, (mono-C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy or halo)-(phenyl, phenoxy, phenylthio, phenylsulfonyl or phenoxy sulfonyl), C<sub>2</sub>-C<sub>6</sub> alkanoylamino, benzoylamino, diphenylmethylamino(C<sub>1</sub>-C<sub>3</sub> alkyl), aminocarbonyl, C<sub>1</sub>-C<sub>3</sub> alkylaminocarbonyl, di(C<sub>1</sub>-C<sub>3</sub> alkyl)aminocarbonyl, halo-C<sub>1</sub>-C<sub>6</sub> alkanoyl, aminosulfonyl, C<sub>1</sub>-C<sub>3</sub> alkylaminosulfonyl, di(C<sub>1</sub>-C<sub>3</sub> alkyl)aminosulfonyl, phenyl(oxy or thio)(C<sub>1</sub>-C<sub>3</sub> alkyl), (halo, C<sub>1</sub>-C<sub>3</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> alkoxy)phenyl(oxy or thio) (C<sub>1</sub>-C<sub>3</sub> alkyl), benzoyl, or (amino, C<sub>1</sub>-C<sub>3</sub> alkylamino or di(C<sub>1</sub>-C<sub>3</sub> alkyl)amino)(C<sub>1</sub>-C<sub>3</sub> alkyl);

or an above R<sup>5</sup> group is substituted with a morpholino(C<sub>1</sub>-C<sub>3</sub> alkyl) group, a phenyl(C<sub>1</sub>-C<sub>3</sub> alkyl)piperidinyl group, a phenyl(C<sub>1</sub>-C<sub>3</sub> alkyl)-Piperidinylaminocarbonyl group, a C<sub>2</sub>-C<sub>6</sub> alkanoylaminothiophenyl group, or a (amino, C<sub>1</sub>-C<sub>3</sub> alkylamino or di(C<sub>1</sub>-C<sub>3</sub> alkyl)amino)naphthalenylsulfonylamino group;

or R<sup>5</sup> is a perhalophenyl group;

or a pharmaceutically acceptable salt thereof.

### Description

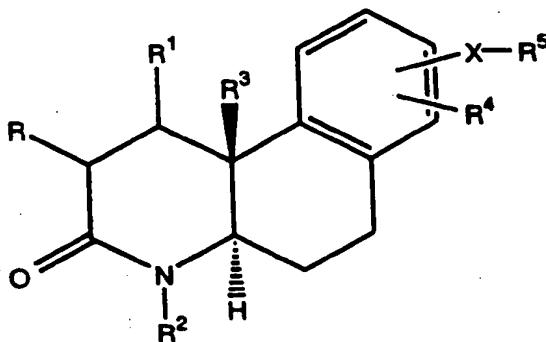
The present invention belongs to the fields of pharmaceutical chemistry and pharmacology, and provides benzo[f]quinolinones which are pharmaceuticals for the inhibition of 5 $\alpha$ -reductase.

It is now widely known that a number of undesirable physiological conditions are androgen-mediated and are dependent on 5 $\alpha$ -dihydrotestosterone (DHT). Such conditions include benign prostatic hyperplasia, male pattern baldness, acne vulgaris, seborrhea, androgenic alopecia, hirsutism and prostate cancer. It has been demonstrated that inhibitors of 5 $\alpha$ -reductase (5AR) block the formation of DHT, because 5AR mediates the conversion of testosterone to the more potent androgen DHT in various target organs. Finasteride, a 5AR inhibitor, is now in the pharmaceutical marketplace and is approved for the treatment of benign prostatic hyperplasia. Mocellini et al., *The Prostate*, 22, 291-99 (1993).

Recently it has been found that there are at least two 5AR isozymes in the human, Andersson *et al.*, Proc. Natl. Acad. Sci. USA, **87**, 3640-44 (1990); Andersson *et al.*, Nature, **354**, 159-61 (1991). The two isozymes, usually called Type I and Type II, exhibit differences in their biochemical properties, genetics and pharmacology. Both isozymes are now the subject of considerable research and it has been found that Type I is more prevalent in the scalp and is more involved in conditions such as androgenic alopecia, and that Type II is more prevalent in the prostate. In prostate, Type I is exclusive to the epithelial compartment in normal, benign hyperplastic and cancerous cells, and the Type II isoform predominates in the fibromuscular stroma.

The present invention provides a series of new compounds which are effective inhibitors of 5AR; many of the compounds are effective inhibitors of both of the 5AR isozymes.

The present invention provides benzo[f]quinolinones of the formula



wherein

R and R<sup>1</sup> both represent hydrogen or combine to form a bond;

R<sup>2</sup> represents hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl;

**R<sup>3</sup>** represents methyl or ethyl;

$R^4$  and  $-X-R^5$  each occupies one of the 7-, 8- and 9-positions;

$R^4$  represents hydrogen, halo, methyl or ethyl;

X represents C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, a bond, -SO<sub>2</sub>, -SO<sub>2</sub><sup>-</sup>, CO-Y-(CH<sub>2</sub>)<sub>n</sub>, -Y-CO-(CH<sub>2</sub>)<sub>n</sub>-CO-, -Z-(CH<sub>2</sub>)<sub>n</sub>, or -SO<sub>3</sub><sup>-</sup>; wherein X groups which are not symmetrical may be in either orientation;

Y represents -S-, -O-, or -NH-;

Z represents -O- or -S-;

**n represents 0-3;**

$R^5$  represents phenyl, naphthalenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, anthracenyl, acenaphthindenyl, thiazolyl, benzimidazolyl, indazolyl, thiophenyl, phenanthrenyl, quinolinyl, fluorenyl, isoquinolinyl, indanyl, benzopyranyl, benzisouquinolinyl, benzindolyl, benzothiazolyl, benzothiophenyl, quinoxalinyl, benzoxazolyl, tetrazolyl, naphthoindolyl, quinazolinyl, thiazolopyridinyl, pyridazinoquinazolinyl, benzisothiazolyl, benzodioxolyl, benzodioxinyl, diphenylmethyl or triphenylmethyl;

the above R<sup>5</sup> groups are unsubstituted or substituted with 1-3 groups chosen from the group consisting of halo, trifluoromethyl, trifluoroethoxy, C<sub>1</sub>-C<sub>4</sub> alkyl, trifluoromethoxy, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, nitro, C<sub>1</sub>-C<sub>3</sub> alkylthio, C<sub>1</sub>-C<sub>6</sub> alkanoyl, phenyl, oxo, phenoxy, phenylthio, C<sub>1</sub>-C<sub>3</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, cyano, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, diphenylmethylamino, triphenylmethylamino, benzyloxy, benzylthi, (mono-halo, nitro or CF<sub>3</sub>)benzyl(oxy or thio), di(C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or C<sub>4</sub>-C<sub>8</sub> cycloalkylalkyl)amino, (mono-C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy or halo)-(phenyl, phenoxy, phenylthio, phenylsulfonyl or phenoxy sulfonyl), C<sub>2</sub>-C<sub>6</sub> alkanoylamino, benzoylamino, diphenylmethylamino(C<sub>1</sub>-C<sub>3</sub> alkyl), aminocarbonyl, C<sub>1</sub>-C<sub>3</sub> alkylaminocarbonyl, di(C<sub>1</sub>-C<sub>3</sub> alkyl)aminocarbonyl, halo-C<sub>1</sub>-C<sub>6</sub> alkanoyl, aminosulfonyl, di(C<sub>1</sub>-C<sub>3</sub> alkylaminosulfonyl, di(C<sub>1</sub>-C<sub>3</sub> alkyl)aminosulfonyl, phenyl(oxy or thio)(C<sub>1</sub>-C<sub>3</sub> alkyl), (halo, C<sub>1</sub>-C<sub>3</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> alkoxy)phenyl(oxy or thio)(C<sub>1</sub>-C<sub>3</sub> alkyl), benzoyl, or (amino, C<sub>1</sub>-C<sub>3</sub> alkylamino or di(C<sub>1</sub>-C<sub>3</sub> alkyl)amino)(C<sub>1</sub>-C<sub>3</sub> alkyl);

or an above R<sup>5</sup> group is substituted with a morpholino(C<sub>1</sub>-C<sub>3</sub> alkyl) group, a phenyl(C<sub>1</sub>-C<sub>3</sub> alkyl)piperidinyl group, a phenyl(C<sub>1</sub>-C<sub>3</sub> alkyl)aminocarbonyl group, a C<sub>2</sub>-C<sub>6</sub> alkanoyl-aminothiophenyl group, or a (amino, C<sub>1</sub>-C<sub>3</sub> alkylamino or di(C<sub>1</sub>-C<sub>3</sub> alkyl)amino)naphthalenylsulfonylaminogroup;

5 or R<sup>5</sup> is a perhalophenyl group;

or a pharmaceutically acceptable salt thereof.

The invention also provides pharmaceutical compositions comprising a compound of the above formula in combination with a pharmaceutically acceptable carrier, diluent or excipient.

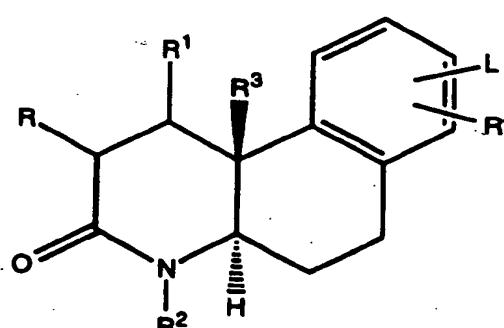
Further, the invention provides a method for inhibiting 5 $\alpha$ -reductase, more preferably, a method for inhibiting both

10 Type I and Type II 5 $\alpha$ -reductase. Further, methods are provided for the treatment of benign prostatic hyperplasia, male pattern baldness, acne vulgaris, seborrhea, androgenic alopecia, hirsutism and prostate cancer, which methods comprise administering an effective amount of a compound of formula I to a patient in need of such treatment. Still further, the invention provides a method for the treatment or prevention of such conditions comprising administering to a patient exhibiting excessive 5AR levels or excessive 5AR activity an effective 5AR-inhibiting amount of a compound of formula I.

15 Still further, the invention provides the use of the compounds of Formula I for inhibiting 5 $\alpha$ -reductase, particularly male pattern baldness, acne vulgaris, seborrhea, androgenic alopecia, hirsutism and prostate cancer is also provided, as is the use of the compounds for the treatment or prevention of such conditions in a patient exhibiting excessive 5AR levels or excessive 5AR activity.

20 The invention further provides a process for preparing a compound of Formula I

(a) wherein an intermediate of the formula



5 is reacted with a compound of the formula



in activated form; or

0 a compound of Formula II in activated form is reacted with a compound of the formula



5 (b) wherein a compound of Formula I wherein X is -Z-(CH<sub>2</sub>)<sub>n</sub>- is prepared by reacting a compound of Formula II with a compound of the formula



2 or a compound of Formula II wherein -L has been replaced by -Z is reacted with a compound of the formula



3 (c) wherein a compound of Formula I wherein X is -CO-Y-(CH<sub>2</sub>)<sub>n</sub>- or -Y-CO-(CH<sub>2</sub>)<sub>n</sub>- is prepared by reacting a compound of Formula II wherein -L has been replaced with one of -YH, -CO-L, -(CH<sub>2</sub>)<sub>n</sub>-YH, or -(CH<sub>2</sub>)<sub>n</sub>-CO-L, with a compound of one of the formula



HY-(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup> or

L-CO-(CH<sub>2</sub>)<sub>n</sub>-R<sup>5</sup>,

provided that one reactant has a -YH group and the other an L group, and no more than one reactant has a -(CH<sub>2</sub>)<sub>n</sub>- group;

(d) wherein a compound of Formula I wherein X is alkyl is prepared by reacting a compound of Formula II in activated form with an aldehyde or ketone which provides the residue of -X-R<sup>5</sup>;

(e) wherein a compound of Formula I wherein R<sup>2</sup> is C<sub>1</sub>-C<sub>3</sub> alkyl is prepared by reacting a compound of Formula I wherein R<sup>2</sup> is hydrogen with an alkyl iodide of the formula

R<sup>2</sup>-I;

(f) or oxidizing the product to prepare a compound of Formula I wherein R and R<sup>1</sup> combine to form a bond;

(g) or oxidizing or reducing an X group;

(h) or removing protecting groups;

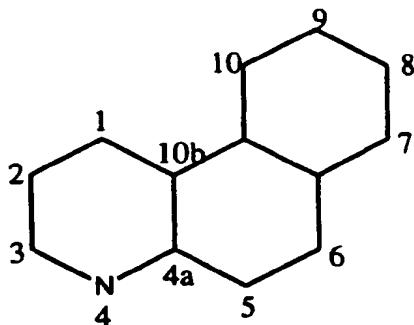
(i) or preparing a salt;

(j) or isolating an optical isomer.

Throughout the present document, all temperatures will be described in degrees Celsius and all expressions of concentration, percentage and proportion will be expressed in weight units, except for mixtures of solvents, which will be described in volume units, unless otherwise stated.

References to compounds of formula I in this document include the pharmaceutically acceptable salts of such compounds, unless otherwise stated.

The various positions on the benzo[f]quinoline ring are indicated below.



The spatial configuration of the group R<sup>3</sup> at 10b and the hydrogen atom at 4a are required, and the synthetic methods for obtaining that configuration will be shown. The reader will understand that most of the compounds can exist in two stereochemical forms, or even more depending on the nature of the R<sup>5</sup> group, and that all stereochemical forms are included in the present invention. In some of the compounds prepared or described below, single enantiomers are prepared in pure form and are identified by (+) or (-) nomenclature. In other cases, the mixture of diastereomers is prepared.

The groups R<sup>4</sup> and X-R<sup>5</sup> may occupy either the 7, 8, or 9-position.

The term "halo" includes chloro, bromo and fluoro.

The various alkyl groups, such as C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl and the like include groups such as methyl, ethyl, propyl, isopropyl, t-butyl, butyl and isobutyl. When such groups link other portions of a molecule, they are bivalent and the location of the linkages will be indicated in the chemical name.

Alkenyl and alkynyl groups constitute linking groups which are bivalent and are bonded to two other groups. For example, C<sub>2</sub>-C<sub>4</sub> alkenyl includes 2-propenyl, 3-but enyl and 2-but enyl; and C<sub>2</sub>-C<sub>4</sub> alkynyl includes, for example, ethynyl, 2-propynyl, 2-butynyl and iso-2-butynyl.

The groups C<sub>1</sub>-C<sub>6</sub> alkanoyl and C<sub>2</sub>-C<sub>6</sub> alkanoyl include such groups as formyl, acetyl, propionyl, isobutyryl, 2-ethyl-

propionyl and hexanoyl. The group C<sub>3</sub>-C<sub>6</sub> cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, and the group C<sub>4</sub>-C<sub>8</sub> cycloalkylalkyl includes, for example, cyclopropylmethyl, cyclohexylethyl, cyclobutylbutyl and cyclohexylmethyl.

5 Terms such as C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, benzylthio, phenoxy, and C<sub>1</sub>-C<sub>3</sub> alkylamino refer to the indicated alkyl, benzyl or the like group linked to an oxygen atom, sulfur atom, sulfonyl group or amino group as indicated.

Terms such as halo-C<sub>1</sub>-C<sub>6</sub> alkanoyl, halophenyl or C<sub>1</sub>-C<sub>3</sub> alkylphenyl refer to the indicated basic group having substituted on it 1, 2, or 3 halo or C<sub>1</sub>-C<sub>3</sub> alkyl groups as may be described in the individual case.

The term perhalophenyl refers to a phenyl group which is fully substituted at all available positions with halogen atoms.

10 The compounds of formula I all have the benzo[f]quinoline nucleus, on the phenyl ring of which is substituted a cyclic group, frequently an arylcyclic group, which is linked to the benzoquinoline through the X linker, which in many cases is simply a bond. The R<sup>5</sup> groups may be substituted with additional organic groups, and may bear as many as three of the indicated substituent groups. Multiple substituents may all be the same, as, for example, 2,3,5-trifluorophenyl, or may be different, such as, for example, 3,5-bis(t-butyl)-4-hydroxyphenyl. The specifically named compounds which appear below in this document will further illustrate the contemplated X, R<sup>5</sup> and substituent groups.

15 The X groups which are not symmetrical may be in either orientation on the molecule; for example, the atom Z of the group -Z-(CH<sub>2</sub>)<sub>n</sub>- may be adjacent either to R<sup>5</sup> or to the phenyl ring of the nucleus of formula I.

The cyclic R<sup>5</sup> groups may take any permissible orientation. For example, the following specific R<sup>5</sup> groups are contemplated.

20 phenyl  
2-quinolinyl  
4-quinolinyl  
7-quinolinyl  
1-isoquinolinyl  
25 3-isoquinolinyl  
8-isoquinolinyl  
2-quinoxaliny  
5-quinoxaliny  
7-quinoxaliny  
30 2-benzothiazolyl  
4-benzothiazolyl  
6-benzothiazolyl  
7-1H-indazolyl  
35 3-1H-indazolyl  
5-2H-indazolyl  
2-2H-indazolyl  
7-2H-indazolyl  
4-3H-indazolyl  
3-3H-indazolyl  
40 1-indolyl  
3-indolyl  
3-2H-indolyl  
2-3H-indolyl  
6-2H-indolyl  
45 4-3H-indolyl  
2-benzoxazolyl  
5-benzoxazolyl  
3-1,2-benzisothiazolyl  
50 5-1,2-benzisothiazolyl  
7-2,1-benzisothiazolyl  
4-2,1-benzisothiazolyl  
2-pyridinyl  
4-pyridinyl  
3-pyridazinyl  
55 5-pyridazinyl  
2-pyrazinyl  
5-pyrazinyl  
2-naphtho[2,3-d]thiazolyl

8-naphtho[2,3-d]thiazolyl  
 6-naphtho[2,3-d]thiazolyl  
 1-naphtho[2,1-d]thiazolyl  
 5-naphtho[2,1-d]thiazolyl  
 5  
 2-naphtho[1,2-d]thiazolyl  
 6-naphtho[1,2-d]thiazolyl  
 1-naphthalenyl  
 2-naphthalenyl  
 2-thienyl  
 10  
 3-thienyl  
 1-anthracenyl  
 10-anthracenyl  
 6-anthracenyl  
 15  
 1-phenanthrenyl  
 4-phenanthrenyl  
 9-phenanthrenyl  
 1-3H-fluorenyl  
 3-3H-fluorenyl  
 9-3H-fluorenyl  
 20  
 1-fluorenyl  
 5-fluorenyl  
 1-acenaphthalenyl  
 5-acenaphthalenyl  
 diphenylmethyl  
 25  
 triphenylmethyl  
 2-thiazolyl  
 4-thiazolyl  
 2-benzimidazolyl  
 6-benzimidazolyl  
 30  
 1-indanyl  
 4-indanyl  
 3-2H-1-benzopyranyl  
 7-2H-1-benzopyranyl  
 2-chromanyl  
 35  
 5-chromanyl  
 4-4H-1-benzopyranyl  
 8-4H-1-benzopyranyl  
 3-5H-1-benzopyranyl  
 5-5H-1-benzopyranyl  
 40  
 1-benz[g]isoquinoliny  
 5-benz[g]isoquinoliny  
 8-benz[g]isoquinoliny  
 4-benz[h]isoquinoliny  
 10-benz[h]isoquinoliny  
 45  
 2-benz[f]isoquinoliny  
 6-benz[f]isoquinoliny  
 3-1H-benz[de]isoquinoliny  
 9-1H-benz[de]isoquinoliny  
 4-4H-benz[de]isoquinoliny  
 50  
 6-4H-benz[de]isoquinoliny  
 1-1H-benz[f]indolyl  
 4-1H-benz[f]indolyl  
 2-3H-benz[f]indolyl  
 7-3H-benz[f]indolyl  
 55  
 2-pyrimidinyl  
 5-pyrimidinyl  
 1-3H-carbazolyl  
 5-3H-carbazolyl

3-4aH-carbazolyl  
 4a-4aH-carbazolyl  
 2-8aH-carbazolyl  
 7-8aH-carbazolyl  
 5  
 8-carbazolyl  
 4-carbazolyl  
 2-1H-benz[g]indolyl  
 6-1H-benz[gl]indolyl  
 3-3H-benz[g]indolyl  
 10 9-3H-benz[g]indolyl  
 1-1H-benz[e]indolyl  
 5-1H-benz[e]indolyl  
 3-3H-benz[e]indolyl  
 7-3H-benz[e]indolyl  
 15 2-benz[cd]indolyl  
 5-benz[cd]indolyl  
 2-1-benzothiophenyl  
 5-1-benzothiophenyl  
 1-2-benzothiophenyl  
 20 7-2-benzothiophenyl  
 5-1H-tetrazolyl  
 1-1H-tetrazolyl  
 5-2H-tetrazolyl  
 25 2-quinazolinyl  
 6-quinazolinyl  
 2-thiazolo[4,5-b]pyridinyl  
 6-thiazolo[4,5-b]pyridinyl  
 7-thiazolo[5,4-b]pyridinyl  
 4-thiazolo[4,5-c]pyridinyl  
 30 6-thiazolo[4,5-c]pyridinyl  
 3-5H-thiazolo[3,2-a]pyridinyl  
 8-5H-thiazolo[3,2-a]pyridinyl  
 2-7H-thiazolo[3,2-a]pyridinyl  
 7-7H-thiazolo[3,2-a]pyridinyl  
 35 3-3H-thiazolo[3,4-a]pyridinyl  
 5-3H-thiazolo[3,4-a]pyridinyl  
 10-10H-pyridazino[3,2-b]quinazolinyl  
 4-10H-pyridazino[3,2-b]quinazolinyl  
 8-10H-pyridazino[3,2-b]quinazolinyl  
 40 3-3H-1,2-benzodioxolyl  
 5-3H-1,2-benzodioxolyl  
 2-1,3-benzodioxolyl  
 7-1,2-benzodioxolyl  
 2-1,4-benzodioxinyl  
 45 6-1,4-benzodioxinyl

Linking X groups, besides the alkyl, alkenyl and alkynyl groups, include the following, for example. The groups are named as they appear in the generic formula, but it will be understood that the groups may, in fact, be oriented in either direction.

50 acetylthio  
 sulfinyl  
 sulfonyl  
 oxycarbonyl  
 propoxycarbonyl  
 methylthiocarbonyl  
 55 butyryl amino  
 propionyloxy  
 ethylaminocarbonyl  
 carbonyl

oxy  
thio  
methoxy  
propylthio  
a bond  
oxysulfonyl

5 The cyclic R<sup>5</sup> groups may be substituted with a variety of substituent groups, as set out in general in formula I. To assure that the reader fully understands the nature of those substituent groups, a representative group of them will be named as follows:

10 chloro  
bromo  
fluoro  
trifluoromethyl  
methyl  
15 isopropyl  
s-butyl  
trifluoromethoxy  
hydroxy  
methoxy  
20 isopropoxy  
nitro  
methylthio  
ethylthio  
formyl  
25 acetyl  
propionyl  
pentanoyl  
2,2-dimethylbutyryl  
phenyl  
30 oxo  
phenoxy  
phenylthio  
methylsulfinyl  
35 propylsulfinyl  
ethylsulfonyl  
isopropylsulfonyl  
cyano  
amino  
methylamino  
40 propylamino  
diphenylmethylamino  
triphenylmethylamino  
benzyloxy  
benzylthio  
45 3-chlorobenzyloxy  
4-fluorobenzylthio  
2-nitrobenzyloxy  
3-trifluoromethylbenzylthio  
dimethylamino  
50 diethylamino  
di(isopropyl)amino  
bis(cyclopropyl)amino  
bis(cyclohexyl)amino  
methyl(cyclohexyl)amino  
55 bis(cyclohexylmethyl)amino  
propyl(cyclopentylethyl)amino  
cyclopentyl(cyclopropylpropyl)amino  
3-methylphenyl

2-propylphenoxy  
 4-ethylphenylthio  
 3-isopropylphenylsulfonyl  
 4-methoxyphenyl  
 5 2-ethoxyphenoxy sulfonyl  
 3-ethoxyphenylthio  
 4-chlorophenyl  
 4-bromophenylthio  
 3-fluorophenoxy sulfonyl  
 10 acetyl amino  
 propionyl amino  
 pentanoyl amino  
 2-ethylpropionyl amino  
 benzoyl amino  
 15 diphenylmethylaminomethyl  
 3-(diphenylmethylamino)propyl  
 aminocarbonyl  
 methylaminocarbonyl  
 20 isopropylaminocarbonyl  
 dimethylaminocarbonyl  
 ethyl(isopropyl)aminocarbonyl  
 chloroacetyl  
 3-bromopropionyl  
 4,4,4-trifluorobutyl  
 25 3-chloro-2-methylbutyl  
 3,4-dichlorohexanoyl  
 aminosulfonyl  
 methylaminosulfonyl  
 30 isopropylaminosulfonyl  
 diethylaminosulfonyl  
 methyl(propyl)aminosulfonyl  
 phenoxy methyl  
 2-phenylthioethyl  
 2-phenoxypropyl  
 35 3-chlorophenylthiomethyl  
 2-(3,4-difluorophenoxy)ethyl  
 2-(2-methoxy-4-propylphenoxy)ethyl  
 3-(3,5-diethoxyphenoxy)propyl  
 40 3-(4-chloro-3-ethoxyphenylthio)propyl  
 2,6-dichloro-4-propylphenylthiomethyl  
 benzoyl  
 aminomethyl  
 45 2-aminoisopropyl  
 methylaminomethyl  
 2-ethylaminoethyl  
 3-(ethylamino)propyl  
 dimethylaminomethyl  
 ethyl(isopropyl)aminomethyl  
 50 3-(ethyl(propyl)amino)propyl  
 morpholinylmethyl  
 2-morpholinylpropyl  
 3-phenylmethyl-1-piperidinyl  
 4-(2-phenylpropyl)-1-piperidinyl  
 55 2-phenylmethyl-1-piperidinylaminocarbonyl  
 4-(3-phenylpropyl)-1-piperidinylaminocarbonyl  
 3-acetyl amino-5-thiophenyl  
 2-hexanoyl amino-4-thiophenyl  
 3-butyryl amino-4-thiophenyl

8-amino-2-naphthalenylsulfonylamino  
 2-methylamino-1-naphthalenylsulfonylamino  
 5-isopropylamino-2-naphthalenylsulfonylamino  
 4-dimethylamino-2-naphthalenylsulfonylamino  
 5  
 3-methyl(propyl)amino-1-naphthalenylsulfonylamino  
 perfluorophenyl  
 perbromophenyl

10 While all of the compounds described by formula I are important in the concept of the present invention, certain groups of those compounds constitute preferred aspects of the invention. The following table sets out a number of such preferred groups, each of which constitutes a preferred aspect of the invention, and the formulations, methods of use and the like associated with each such group are also preferred aspects. It will be understood that the reader can combine groups of preferred aspects listed in the following table to produce additional more limited or more comprehensive preferred aspects.

15 a) R and R<sup>1</sup> both represent hydrogen;

b) R<sup>3</sup> represents methyl;

20 c) R<sup>2</sup> represents C<sub>1</sub>-C<sub>3</sub> alkyi;

d) R<sup>2</sup> represents C<sub>1</sub>-C<sub>2</sub> alkyl;

e) R<sup>2</sup> represents methyl;

25 f) R<sup>2</sup> represents methyl or hydrogen;

g) R<sup>4</sup> represents hydrogen;

30 h) R<sup>4</sup> represents hydrogen, halo or methyl;

i) X represents alkyl, alkenyl or alkynyl;

j) X represents a bond;

35 k) X represents a bond or a sulfur atom;

l) X represents -SO-, -SO<sub>2</sub>-, or -SO<sub>3</sub>-;

40 m) X represents -CO- or -CO-Y-(CH<sub>2</sub>)<sub>n</sub>-;

n) X represents -Z-(CH<sub>2</sub>)<sub>n</sub>-, alkyl or -CO-;

o) X represents a bond, -Z-(CH<sub>2</sub>)<sub>n</sub>-, alkyl or -CO-;

45 p) X represents a sulfur atom;

q) Y represents -O- or -S-;

r) Y represents -NH-;

50 s) n represents 0 or 1;

t) n represents 2 or 3;

55 u) n represents 0;

v) Z represents -S-;

- w)  $R^5$  represents phenyl or naphthalenyl;
- x)  $R^5$  represents pyridinyl, pyrazinyl, pyridazinyl or pyrimidinyl;
- 5 y)  $R^5$  represents anthracenyl, phenanthrenyl, fluorenyl or acenaphthalenyl;
- z)  $R^5$  represents thiazolyl, thiophenyl or tetrazolyl;
- 10 aa)  $R^5$  represents benzimidazolyl, indanyl, indolyl or indazolyl;
- ab)  $R^5$  represents quinolinyl, isoquinolinyl, quinoxalinyl or quinazolinyl;
- 15 ac)  $R^5$  represents benzopyranyl, benzothiazolyl, benzothiophenyl or benzisothiazolyl;
- ad)  $R^5$  represents benzothiazolyl;
- ae)  $R^5$  represents benzoxazolyl, benzodioxolyl, or benzodioxinyl;
- 20 af)  $R^5$  represents benzisoquinolyl, benzindolyl, naphthothiazolyl, thiazolopyridinyl or pyridazinoquinazolinyl;
- ag)  $R^5$  represents diphenylmethyl or triphenylmethyl.

Further preferred classes of compounds are also important in the practice of the present invention. A particularly preferred class of compounds includes those wherein  $R^2$  represents methyl or hydrogen, particularly methyl; X represents a bond, a sulfur atom or an ethenyl group, particularly a bond or a sulfur atom;  $R^5$  represents phenyl, naphthalenyl, isoquinolinyl, indolyl, benzothiazolyl, pyridinyl, indazolyl, thiazolopyridinyl, quinolinyl or diphenylmethyl; and the  $R^5$  group is unsubstituted or substituted with 1-3, particularly 1, groups chosen from the group consisting of halo, trifluoromethoxy, trifluoroethoxy, trifluoromethyl,  $C_1$ - $C_3$  alkyl, methoxy, nitro, phenyl, toluenesulfonyl, and pivaloylamino.

A further preferred class of compounds of the present invention includes those described in the paragraph immediately above, and, in addition, those wherein X represents propyl, aminocarbonylmethyl, methoxycarbonyl and oxy carbonyl;  $R^5$  represents thiophenyl, fluorenyl, indanyl, quinoxalinyl, pyridazinyl, thiazolopyridinyl, and benzisoquinolinyl; and the  $R^5$  group is unsubstituted or substituted with 1-3, particularly 1, groups chosen from the group consisting of hydroxy,  $C_1$ - $C_4$  alkyl, oxo, benzyloxy, phenoxy methyl and benzylpiperidinyl.

As described in formula I, the invention includes pharmaceutically acceptable salts of the compounds defined by the above formula. Although generally neutral, a particular compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of nontoxic inorganic bases, and nontoxic inorganic and organic acids, to form a pharmaceutically acceptable salt. Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

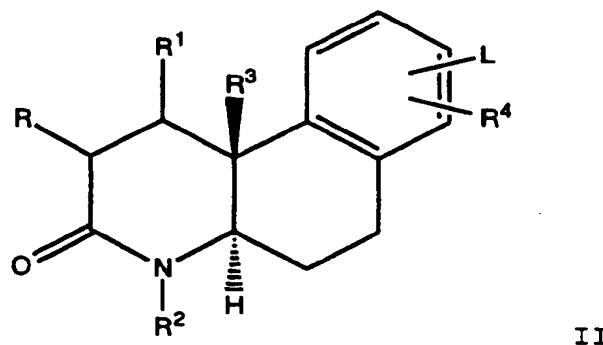
Base addition salts include those derived from nontoxic inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate. The potassium and sodium salt forms are particularly preferred.

Thus, the groups  $R^4$  and X- $R^5$  include a number of substitutions each of which may be placed at the 7, 8 or 9-position of the nucleus of formula I. All such substituents are easily understandable by the chemist, but a number of the contemplated substituent arrangements will be mentioned for the convenience of the reader.

8-(phenoxy sulfonyl)-4-quinolinyloxy

7-chloro-8-(3-chloromethyl-7-quinolinylothio)

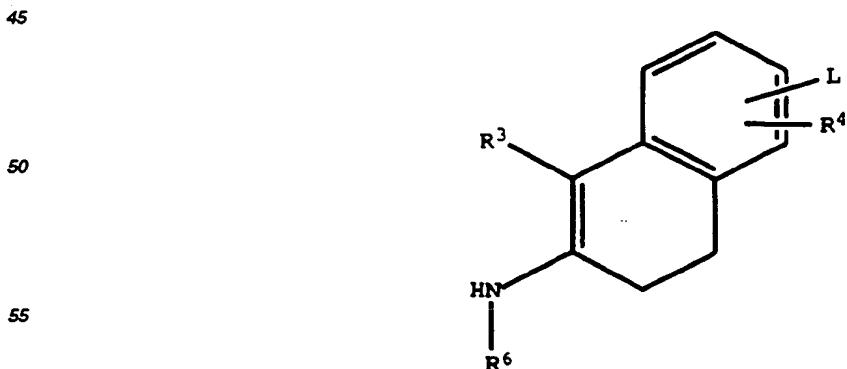
7-[2-(3-phenoxy-6-isoquinolylaminocarbonyl)ethyl]  
 9-fluoro-7-(1-methoxycarbonyl-4-isoquinolylmethyl)  
 8-[3-(5-bromo-*t*-butyl-3-quinoxalinyl)propyl]  
 8-fluoro-7-[3-(8-butylthio-2-quinoxalinyl)-3-propynyl]  
 5 7-(3-phenyl-1,2-benzisothiazol-5-yloxycarbonyl)  
 8-bromo-9-(5-hexyloxysulfonylbenzoxazol-2-ylthio)  
 9-methyl-7-(6-trifluoromethyl-2,1-benzisothiazol-3-yl)  
 7-(3-isopropoxycarbonylaminopyridinyl-2-ylmethyl)  
 9-chloro-8-(7-hydroxy-4-benzothiazolylthio)  
 10 7-(4-isopentoxycarbonyl-1H-indazol-4-yloxy)  
 7-ethyl-9-[3-(6-[2-ethyl-5-methylphenoxy)sulfonyl]-1H-indazol-3-yl)-2-propynyl]  
 9-[2-(6-ethoxycarbonyl-2H-indazol-2-yloxy)ethyl]  
 8-[2-(3-fluoro-2H-indazol-6-yl)ethoxy]  
 9-chloro-7-(3-trifluoromethoxy-3H-indazol-4-yl-thiocarbonylmethyl)  
 15 7-[2-(5-propoxy-4-[4-fluorophenoxy]-3H-indazol-7-ylthio)ethyl]  
 8-ethyl-7-[4-(4-[3-chlorophenoxy)sulfonyl]-2-indolyl)butyl]  
 8-[3-(7-methoxy-4-[2,3-dichloropropoxycarbonyl-amino]2-indolyl)propyl]  
 7-[2-(5-[4-fluoro-3-methylphenoxy)sulfonyl]-2H-indol-4-yl)ethylcarbonylthio]  
 20 8-methoxy-7-[3-(6-chloro-2-[3-chloro-5-ethoxyethoxyethyl]-2H-indol-3-yl)-2-butynyl]  
 25 Synthesis of the compounds of formula I may proceed in various ways, depending in large part on the identity of the group -X-R<sup>5</sup>. It is very often advantageous to form the benzo[f]quinoline nucleus without the -X-R<sup>5</sup> group, and to add that group in a separate step, thus providing a convergent synthesis. In such a case, the -X-R<sup>5</sup> group of the compound of formula I is replaced by a leaving group, preferably a chlorine or bromine atom, when the benzo[f]quinoline nucleus is prepared. Since the R<sup>4</sup> group of the nucleus is small, it may be in place throughout the synthesis. Thus, an important intermediate is the following compound of formula II.



40 wherein L represents a leaving group, preferably chloro or bromo.

A series of synthetic methods for the preparation of intermediates of formula II was taught by Audia *et al.* in U.S. Patent 5,239,075, issued August 24, 1993. That patent is incorporated by reference herein, and the reader readily will understand the synthetic methods taught by it.

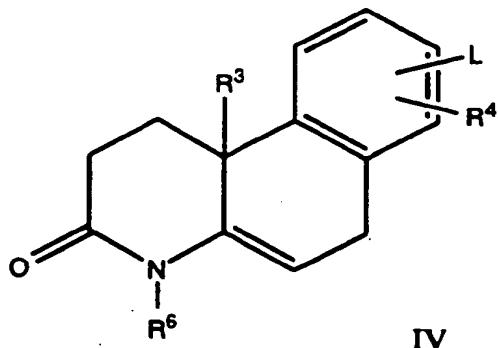
A preferred method for preparing the intermediates of formula II is the heteroannulation carried out by reacting an enamine of the formula



with an acryloyl halide, particularly acryloyl chloride, acrylic anhydride, or acryloyl toluenesulfonate or methanesulfonate.

EP 0 703 221 A1

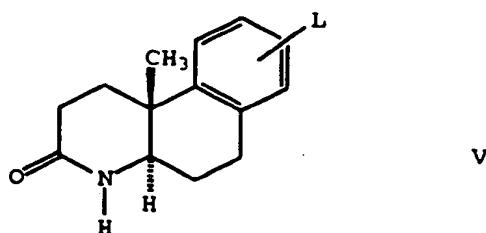
intermediate is a chiral directing group, in order to obtain the correct enantiomer of the The most preferred R<sup>6</sup> group is (R)-(+)-1-phenylethyl. This process is taught in general by  
troannulation just described is of the formula



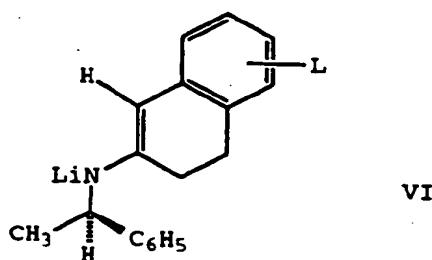
1a,5- position must be reduced in a second step. The reduction is readily carried out under  
ll reducing agents such as borohydrides. Cyanoborohydride is preferred; the reduction may  
in formic acid under ambient conditions. More conveniently, the reduction step may be  
of the R<sup>6</sup> group, by reaction with trifluoroacetic acid in a reaction medium containing or  
reduced temperature in the range of from about -40° to 0°.  
ation is carried out under mild process conditions. In most instances it will be found that  
in short periods of time at temperatures in the range of ambient. For example, temperatures  
are used, and reaction times in the range from a few minutes to a few hours are sufficient.  
ures are in the range from about -20° to about ambient temperature, and most preferably  
at very low temperatures in the range of -20° to -80°, and the reaction mixture is allowed  
perature while the reaction occurs. The reaction mixture may be a biphasic mixture of a  
nd an aqueous solution of a mild base. For example, solvents may include haloalkanes,  
uran, and nitriles including acetonitrile. Preferred mild bases are alkali metal carbonates  
ly basic reagents, such as alkali and alkaline earth metal hydroxides and the like may be  
re usually preferred.

method of synthesis of a key intermediate of formula II proceeds according to the following

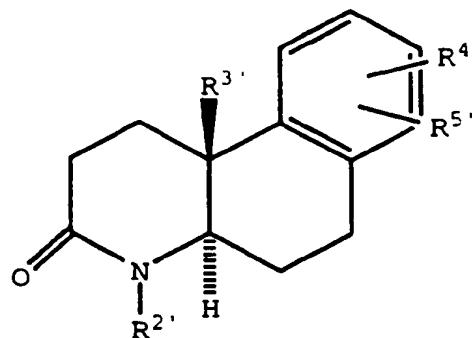
rmula



and is located at the 7-, 8- or 9-position is prepared by reacting a compound of the formula



solvent to prepare a compound of the formula



wherein R<sup>2</sup> is methyl, ethyl or n-propyl;

15 R<sup>3</sup> is hydrogen or methyl;

R<sup>4</sup> is hydrogen, halo, methyl or ethyl;

R<sup>5</sup> is halo, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl or C<sub>1</sub>-C<sub>6</sub> alkoxy;

20 or R<sup>5</sup> is a group -A-R<sup>6</sup> wherein A is C<sub>1</sub>-C<sub>6</sub> alky, C<sub>2</sub>-C<sub>6</sub> alkenyl, or C<sub>2</sub>-C<sub>6</sub> alkynyl; and R<sup>6</sup> is halo, trifluoromethyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy;

or R<sup>5</sup> is a group -X'-R<sup>7</sup> wherein X' is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl or a bond;

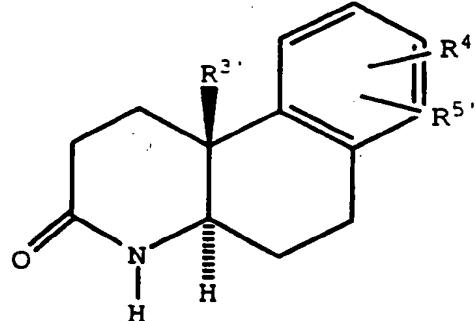
25 and R<sup>7</sup> is phenyl, naphthalenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, anthracenyl, acenaphthalenyl, thiazolyl, benzimidazolyl, indazolyl, thiophenyl, phenanthrenyl, quinolinyl, fluorenyl, isoquinolinyl, indanyl, benzopyranyl, indolyl, benzisoquinolinyl, benzindolyl, benzothiazolyl, benzothiophenyl, quinoxalinyl, benzoxazolyl, tetrazolyl, naphthothiazolyl, quinazolinyl, thiazolopyridinyl, pyridazinoquinazolinyl, benzothiazolyl, benzodioxolyl, benzodioxinyl, diphenylmethyl or triphenylmethyl;

the above R<sup>7</sup> groups are unsubstituted or substituted with 1-3 groups chosen from the group consisting of halo, trifluoromethyl, trifluoroethoxy, C<sub>1</sub>-C<sub>4</sub> alkyl, trifluoromethoxy, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, nitro, C<sub>1</sub>-C<sub>3</sub> alkylthio, C<sub>1</sub>-C<sub>6</sub> alkanoyl, phenyl, oxy, phenoxy, phenylthio, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, cyano, benzyloxy, benzylthio, (mono-<sup>30</sup>halo, nitro or trifluoromethyl)benzyl(oxy or thio), (mono-C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy or halo)-(phenyl, phenoxy, phenylthio, phenylsulfonyl or phenoxy)sulfonyl), halo-C<sub>1</sub>-C<sub>6</sub> alkanoyl, phenyl(oxy or thio)(C<sub>1</sub>-C<sub>3</sub> alkyl), (halo, C<sub>1</sub>-C<sub>3</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> alkoxy)phenyl(oxy or thio)(C<sub>1</sub>-C<sub>3</sub> alkyl), or benzoyl;

or an above R<sup>7</sup> group is substituted with a morpholino(C<sub>1</sub>-C<sub>3</sub> alkyl) group, or a phenyl(C<sub>1</sub>-C<sub>3</sub> alkyl)piperidinyl group;

or R<sup>7</sup> is a perhalophenyl group;

35 the process comprises reacting a compound of the formula



with methyl, ethyl or n-propyl iodide in a reaction mixture comprising an organic solvent chosen from the group consisting of tetrahydrofuran, dimethoxyethane, diethoxyethane and methyl t-butyl ether, and aqueous sodium or potassium hydroxide.

The compounds prepared by the alkylation process are among those which have been described in full above, or have been described in full in the above-mentioned patent. No additional description of the products is necessary. Similarly, the starting materials of Formula B have also been thoroughly described, and they are prepared by the general methods of preparation described in this document or in U.S. 5,239,075.

The present process itself is readily carried out, and is distinguished by both particularly effective alkylation, under mild and easily controlled conditions, and by particularly easy isolation of the products. Frequently, prior art alkylations of similar types required the use of phase transfer catalysts to isolate the products in satisfactory yield and purity, but it

has been found that the products of the present alkylations are isolated by simple crystallization.

Certain aspects of the alkylation process are preferred and will be mentioned below specifically. It will be understood that the following aspects are each important individually, and also that preferred aspects may be combined to create further, more limited or more expansive, preferred aspects.

5

- a) R<sup>2</sup> is methyl and the compound of formula B is reacted with methyl iodide;
- b) R<sup>2</sup> is methyl or ethyl and the compound of formula B is reacted with methyl or ethyl iodide;
- 10 c) R<sup>3</sup> is hydrogen;
- d) R<sup>3</sup> is methyl;
- e) R<sup>4</sup> is hydrogen;
- 15 f) R<sup>5</sup> is halo;
- g) the organic solvent is tetrahydrofuran;
- 20 h) the hydroxide is sodium hydroxide;
- i) the concentration of the aqueous sodium or potassium hydroxide is near saturation.

25

The alkylation process is carried out in conventional chemical plant equipment, preferably at ambient pressure and at moderate temperatures. It is preferably begun by slurring the starting material of formula B in the organic solvent at a temperature near ambient, such as from about 0° to about 50°, more preferably from about 15° to about 25°. The most preferred organic solvent is tetrahydrofuran (THF), and it is preferred to use about 5-15 liters of solvent per kilogram of starting material; more preferable solvent volume is about 10 liters per kilogram. The alkyl iodide is then added as neat liquid. A substantial excess of alkyl iodide is preferably used, such as about 1.2-1.8 equivalents based on the starting material, most preferably about 1.5 equivalents.

30

The aqueous sodium or potassium hydroxide is then added, still at about ambient temperature, in an amount of about 1-4 liters per kilogram of starting material. The quantity of aqueous base is somewhat dependent on the concentration of the base and the choice of sodium or potassium hydroxide; when the most preferred base, 50% sodium hydroxide, is used, the most preferred amount of it is about 2 liters per kilogram of starting material. Then the reaction mixture, consisting of solid material slurried in two liquid phases, is warmed to about 25-65° with vigorous agitation and the reaction is allowed to proceed at about constant temperature with constant agitation. The preferred reaction temperature is about 35-40°. As the reaction proceeds toward completion, the solid starting material and alkyl iodide will dissolve and react, so the disappearance of solids is a crude indication of completion. The reaction may be followed by high pressure liquid chromatography (HPLC) on C-18 silica gel column, eluting with 1:1 acetonitrile:aqueous buffer (5% ammonium acetate) and monitoring at 220 nanometers.

40

When the reaction has gone as far as is desired toward completion, the mixture is cooled to about ambient and the aqueous layer is separated and discarded.

45

The preferred purification and isolation procedure proceeds by diluting the organic layer with water, and neutralizing it with aqueous mineral acid. Then the solution is distilled until the vapor temperature rises to about 69-80°, removing most of the THF. Slow cooling to about 5° over a period of about 1-14 hours crystallizes the product, which needs only washing with water and drying to be ready for use as an intermediate or as a pharmaceutical.

The alkylation process provides product in the same stereochemical form as the starting material, in satisfactory purity for the pharmaceutical industry, and in yields of or above 90% when operated according to the preferred manners.

50

The following Examples further explain the process and provide details which will be of use to the skilled reader.

#### Example 1

(4aR)-(10bR)-8-chloro-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

55

To a 1-liter flask equipped with a condenser and a stirrer were added 470 mL of THF, 18.7 g of methyl iodide and 47 g of (4aR)-(10bR)-8-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one, and stirring was begun at ambient temperature. To the mixture was added 100 mL of 50% aqueous sodium hydroxide in one portion, and gentle heating was begun. The temperature was raised as high as 41° and was then gradually lowered to 29° at the end of 16 hours of stirring. HPLC liquid chromatography, eluting with 1:1 acetonitrile:aqueous buffer (5% ammonium acetate) and mon-

itoring at 220 nanometers, then showed that all the starting material had been consumed and the aqueous layer was removed. The organic layer was concentrated to an oil under vacuum, and the residue was dissolved in ethyl acetate. The solution was washed with brine, and the organic layer was washed with 200 mL of water twice, and was dried over magnesium sulfate and evaporated under vacuum while heptane was added portionwise as the ethyl acetate was removed. A total of 500 mL of heptane was added, and the product began to crystallize when about half of it had been added. The slurry was concentrated to about 300 ml, and filtered, and the solids were washed with heptane and dried in vacuum at 40-50° to obtain 47.03 g of product, m.p. 97-99°, of 98.7% purity.

5 The following example shows an advantageous manner of isolating the product of the present alkylation.

10 Example 1A

(4aR)-(10bR)-8-chloro-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Two hundred L of THF was added to a reactor, and 24.6 kg of (4aR)-(10bR)-8-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was added. Then 35 kg of methyl iodide was added, rinsed in with 10 L of THF. A 79.6 kg portion of 50% aqueous sodium hydroxide was added in 13 minutes at 15-25°, rinsed in with 40 L of THF. The mixture was stirred at 36-39° for 13 hours, and was then cooled to 15-25°. The layers were allowed to separate, and the water/THF phase was neutralized to pH 7 with hydrochloric acid and heated to reflux. Distillate was removed until the temperature reached 77°. A total of 154 kg of water was added from time to time. The solution was cooled over 3 hours to 3-10°, and was then stirred vigorously at that temperature until solids began to form. Then the slurry was stirred gently at constant temperature for 3 hours. The slurry was filtered, and the vessel and filter cake were washed with cold water. The cake was air dried at 25-35° for 75 hours to obtain 27.3 kg of the desired product, potency 85.1% by liquid chromatographic analysis.

25 Example 2

(4aR)-(10bR)-8-chloro-4-ethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

A 9.4 g portion of (4aR)-(10bR)-8-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was combined in a flask with 94 ml of THF, 20 mL of 50% aqueous sodium hydroxide and 9.36 g of ethyl iodide, and was stirred at reflux, about 66°, for about 16 hours. The mixture was cooled to ambient temperature, and the layers were separated. The organic layer was evaporated to an oil, which was dissolved in ethyl acetate and extracted three times with 100 mL portions of water. It was then dried and evaporated to half its volume while heptane was added in portions. The resulting white crystalline product was filtered, washed with heptane and dried under vacuum at 25° to obtain 3.15 g of the desired product, m.p. 108-110°.

35

Analysis calculated for C <sub>15</sub> H <sub>18</sub> ClNO:			
Found:	C, 68.54; C, 68.50;	H, 6.83; H, 6.88;	N, 5.54 N, 5.31

40 Mass spec. (f.d.): M+ 263

Example 3

(4aR)-(10bR)-8-chloro-4-ethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

45 A 9.4 g portion of (4aR)-(10bR)-8-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was combined with 150 mL of THF, 20 mL of 50% aqueous sodium hydroxide and 12.5 g of ethyl iodide in a flask, and was warmed with stirring to about 37°. Stirring at approximately constant temperature was continued for about 72 hours and the reaction was worked up as described above in Example 2 to obtain 3.88 g of the desired product, m.p. 108-110°. The product was found to be 98.6% pure by HPLC, eluting with 1:1 acetonitrile:aqueous buffer (5% ammonium acetate) and monitoring at 220 nanometers.

Example 4

(4aR)-(10bR)-8-chloro-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

55 A 2.35 g portion of (4aR)-(10bR)-8-chloro-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was slurried in 40 mL of THF and 5 mL of 50% aqueous sodium hydroxide, and 3.4 g of propyl iodide was added. The mixture was heated to about 60°, and the mixture was stirred at that temperature for about 22 hours. Workup was carried out by separating the organic layer and evaporating it to dryness, and adding water and ethyl acetate. The organic layer was separated,

washed twice with water, dried, filtered and evaporated under vacuum to obtain 710 mg of white crystalline product, found to be of about 90% purity. It was then purified by silica gel flash chromatography, eluting with ethyl acetate, to obtain 510 mg of purified product, m.p. 110-111°, of 98.98% purity, by HPLC, eluting with 1:1 acetonitrile:aqueous buffer (5% ammonium acetate) and monitoring at 220 nanometers.

5

Analysis calculated for C <sub>16</sub> H <sub>20</sub> NCIO:			
	C, 69.18;	H, 7.26;	N, 5.04
Found:	C, 68.92;	H, 7.09;	N, 5.15

10

If a product of formula I having an isopropyl R<sup>2</sup> group is desired, alkylation of the intermediate of formula VIII may be accomplished with isopropyl iodide, using sodium hydride as an activating agent and operating the reaction in a solvent of the group mentioned just above at an elevated temperature such as the reflux temperature.

15

Frequently a final stage intermediate such as that of formula VIII is produced in a racemic form as a mixture of the two trans-4a-10b isomers. Such an isomeric mixture may be converted to substantially pure desired enantiomers by a process clearly explained in U.S. Patent 5,239,075, which proceeds by opening the piperidinone ring with a strong acid such as methanesulfonic acid, preparing a chiral salt with (-)-(R,R)-di-p-tolyltartaric acid, and separating the desired enantiomeric form of the salt as typically is done in such resolutions. The salt is then sprung with aqueous base and the piperidinone ring is reclosed by simple heating.

20

Another operation which may be carried out on the nucleus of the compounds of the present invention is oxidation to provide the compounds wherein R and R<sup>1</sup> represent a bond. Such oxidations are conveniently carried out by reaction with an oxidizing agent such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of bis(trimethylsilyl) trifluoromethyl acetamide, preferably in dioxane as solvent. The oxidations are carried out at elevated temperature, such as the reflux temperature or from about 50° to about 150°, and preferably the reaction mixtures are stirred at about ambient temperature for a period of time before heating is begun. Further, information about such oxidations can be found below in the Examples.

25

In the course of preparing compounds having various X-R<sup>5</sup> groups, it is necessary or convenient to provide nucleus compounds having corresponding leaving groups or reactive groups. For example, compounds having carboxy, thio, hydroxy, amino, formyl and B(OH)<sub>2</sub> groups are needed for various syntheses and are readily prepared, as is demonstrated below, for example, in the Preparations. Such compounds are preferably prepared from compounds having a halogen atom, particularly a bromine atom but also iodine and chlorine atoms on the nucleus.

30

Various processes are conveniently used for placing the X-R<sup>5</sup> groups on the benzoquinolinone nucleus; the choice of processes is primarily dependent on the nature of the X group. Where the X group is merely a bond, a preferred process is dependent on palladium mediated boron chemistry. In one preferred process, a benzoquinolinone nucleus compound having a bromine atom as the L substituent is reacted with an intermediate which constitutes the R<sup>5</sup> substituent group with a boronic acid (B(OH)<sub>2</sub>) at the point of attachment to the benzoquinolinone nucleus. The reaction is conveniently carried out in the presence of a catalytic amount of tetrakis (triphenylphosphine) palladium, in a basic reaction mixture including, for example, aqueous sodium carbonate or triethylamine. The preferred solvent is an ether such as THF or dimethoxyethane (DME), and the reactions go cleanly at elevated temperatures such as the reflux temperature or from about 50° to about 100°. A useful variation on the above process is carried out using an ester of boronic acid as the intermediate, such as a diethylborane. The examples show illustrations of such syntheses.

35

Similarly, compounds having a bond as the X group may be synthesized by the palladium mediated reaction of a bromine-substituted compound providing the R<sup>5</sup> group with a boronic acid-substituted benzoquinolinone nucleus.

40

Still another method for preparing compounds having no X group is to react a halo-substituted nucleus compound of formula IV with a compound comprising the desired R<sup>5</sup> group, substituted with a tri-n-butylstannyl group at the point of attachment. Such reactions are carried out in the presence of a small amount of bis(triphenylphosphine)palladium halide at high temperatures such as from about 60 to about 120°. A solvent such as acetonitrile may be used, and the reaction should be carried out in inert gas atmosphere.

45

Another particularly important group of compounds of formula I are those wherein X is a sulfur atom. Such groups are conveniently prepared by at least two main processes. In one process, a halo-substituted benzoquinolinone nucleus compound is reacted with a disulfide of the formula R<sup>5</sup>-S-S-R<sup>5</sup>. For example, if a benzylthio substituent is to be provided, the disulfide would be dibenzyldisulfide. The reactions go readily at ambient temperature after combining the reactants at a very low temperature, such as from about -50° to about -100°, in an ether solvent in the presence of a very strong base, particularly a combination of methyl lithium and t-butyl lithium. The reactions are rapid and may be carried out in 1 hour or, at most, a few hours. Another method of synthesis of thiosubstituted compounds, which avoids the use of very low temperatures, is one where either the nucleus or the compound providing the R<sup>5</sup> group is substituted with an SH group and the other is substituted with a bromine, chlorine or iodine atom. Such reactions are carried out at ambient or moderately elevated temperatures, such as from about 50° to about 100°, in a high-boiling solvent such as dimethyl-

formamide and in a basic reaction medium. Such bases as potassium carbonate, sodium bicarbonate, triethylamine and other moderately strong bases are adequate. Numerous examples of such syntheses are shown below.

Similarly, when the group X is an oxygen atom, the compounds are conveniently prepared by reactions where one of the nucleus and the R<sup>5</sup> group - providing compound carries a halogen atom, and the other carries a hydroxy group. As usual with such reactions, basic conditions and moderately elevated temperatures, such as were just described, are adequate to provide reasonably prompt and clean production of the desired compound of formula I.

Compounds wherein X is an oxyalkyl or thioalkyl group are prepared from a nucleus compound having a formyl or formylalkyl L substituent, which material is prepared, as shown below, by reaction of a halo-substituted nucleus compound with dimethylformamide in the presence of a very strong base, to prepare the formyl substituted compound. It is reduced to form a hydroxymethyl group, which is converted to a haloalkyl group, and finally reacted with an SH or OH-substituted compound providing the R<sup>5</sup> group.

The group of compounds of formula I where X is alkyl, alkenyl or alkynyl are made, in general, by processes where a halo-substituted nucleus compound is reacted with a compound providing the X-R<sup>5</sup> group, in the presence of a 9-borabicyclo[3.3.1]nonane alkyl compound (generated in situ by treatment of the appropriate alkene with 9-borabicyclo[3.3.1]nonane (9-BBN)) or of a bis(tri-substituted-phosphine)palladium compound, at a high temperature in an inert atmosphere. Solvents such as dimethylformamide may be used, and a basic environment provided by triethylamine or the like is appropriate. Temperatures in the range of from about 80° to about 140° may be used for long periods of time up to as much as 24 hours. The resulting compounds may be hydrogenated in conventional manners to reduce them from alkynes to alkenes or from alkenes to alkyls.

Another method of synthesis of alkyl-linked compounds may be carried out by reacting the halo-substituted benzoquinoline nucleus compound with a very strong base, preferably a combination of methyl lithium and t-butyl lithium, and then adding an aldehyde or ketone providing the desired X-R<sup>5</sup> substituent. For example, an example below shows the preparation of a compound wherein X is a bond and R<sup>5</sup> is diphenylmethyl by such a reaction of benzophenone. Such reactions should be carried out at low temperature, warming to ambient or slightly elevated temperature, preferably in an ether solvent.

Compounds of formula I wherein X is a carbonyl group, an ester group or a carboxamide are prepared in manners following the general processes for synthesis of such compounds. For example, a compound where X is a carboxamide may conveniently be prepared by reacting a halo-substituted benzoquinolinone nucleus compound with an isocyanate carrying the desired R<sup>5</sup> group. Such reactions are carried out in ether solvents, frequently preferably THF, in the presence of methyl lithium/t-butyl lithium at low temperatures.

Another method for synthesis of carbonyl-substituted compounds is to react an aldehyde with a halo-substituted nucleus compound, to provide a hydroxymethyl-substituted intermediate. Such a reaction is carried out in the presence of methyl lithium/t-butyl lithium at low temperatures, again in an ethereal solvent by preference. The hydroxymethyl intermediate is oxidized, as with Jones reagent under the usual conditions for such reactions, to prepare the desired compound where X is a carbonyl group.

The benzoquinolinone intermediate having a carboxy substituent on the phenyl ring, the preparation of which is shown below as a Preparation, is conveniently used to prepare compounds where X incorporates an ester or amide linkage, by conventional esterification reactions with alcohols, or amide preparations with amines. All of the conventional reaction conditions are applicable, such as the use of carbonyldiimidazole as an initiator, or oxalyl chloride/dimethylformamide. When an X group incorporates an alkylene chain together with an ester or amide linkage, appropriate starting materials including the alkylene chain are used as a chemist would anticipate.

On the other hand, when the X group comprises an amide linkage where the nitrogen is linked to the benzoquinolinone, the amino-substituted intermediate prepared below is conveniently reacted with, for example, a carbonyl halide carrying the desired R<sup>5</sup> group under the conventional reaction conditions. Again, small alkylene groups may be incorporated as desired to make up any of the possible X groups in the contemplation of the present invention.

For example, an unsaturated alkyl-substituted nucleus compound, prepared as discussed above, may be oxidatively cleaved to form the corresponding carboxyalkyl compound. Oxidizing agents such as periodates are commonly used for such transformation and may be used in these instances. The carboxy compound is then esterified or amidated in the usual manner to prepare the desired alkylester or alkyl-amide X group.

It will be understood that the above discussions of esters include thioesters where the group Y represents a sulfur atom, as well as the more commonly used esters.

Finally, numerous transformations are or may be carried out on R<sup>5</sup> groups, to transform one compound of the present invention to another compound. For example, a compound where the R<sup>5</sup> group is substituted with a functional group such as alkanoyl, especially formyl, may be reacted with an amine to prepare the corresponding aminoalkyl-substituted compound. Compounds having, for example, nitro groups may be reduced to form the corresponding amino-substituted compounds, and amino-substituted compounds may be reacted with ketones or aldehydes in the presence of reducing agents, or by subsequent reduction, to prepare the corresponding compounds wherein the R<sup>5</sup> group is substituted with alkyl amino.

Further information about the preparation of compounds of the present invention is to be found in the following Preparations and Examples, which, while certainly not intended to limit the present invention, are illustrative of the processes by which all of the compounds are prepared.

The first group of Preparations below illustrate the preferred synthesis of the benzoquinolinone nucleus compounds which process was described in detail above.

Preparation 1

(R)-6-bromo-2-(1-phenylethylamino)-3,4-dihydronaphthalene, lithium salt

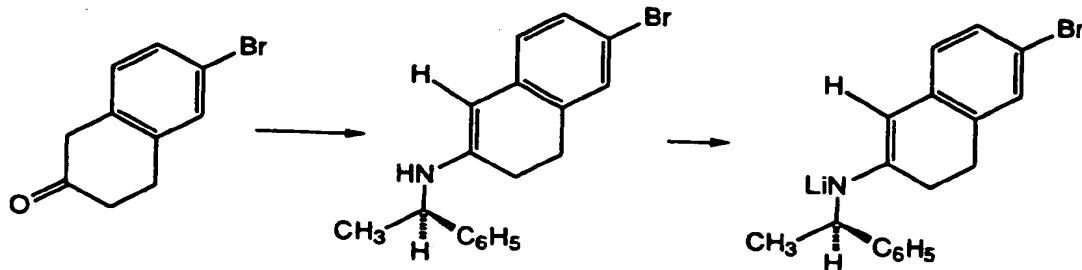
10

15

20

25

30



6-Bromo-2-tetralone, (45.0 g, 200 mmol uncorrected, potency of 90%, 0.90 equiv, corrected) was refluxed with (R)-(+)-phenylethylamine (26.6 g, 220 mmol, 1.10 equiv), *p*-toluenesulfonic acid (160 mg, 0.84 mmol, 0.004 equiv), and toluene (600 mL) in a 2000-mL round bottom flask fitted with a water separator. Reflux was continued until a water-free distillate was observed and then approximately 250 mL of toluene was collected over about 2 to 3 hours. The mixture was cooled to approximately 30-35° and concentrated under house vacuum.

The residue above, containing the enamine intermediate, was dissolved in tetrahydrofuran (THF, 480 g, 540 mL) and cooled below -50°. This solution of the enamine was added via cannula to a solution of lithium diisopropylamide (LDA, 1.15 equiv) at -50 to -60° over 5 minutes. The solution was warmed to -5° over 20 minutes and then recooled to -75° affording a 0.125 M solution of the lithium salt starting material. Proceed immediately to next step - unstable intermediate.

Preparation 2

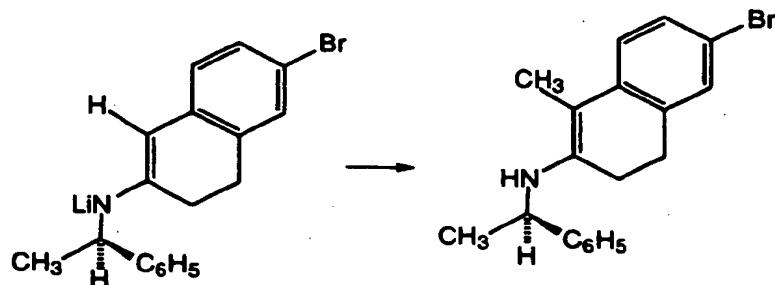
(4a*R*)-10*b**R*)-8-bromo-10*b*-methyl-1,2,3,4,4*a*,5,6,10*b*-octahydrobenzo[*f*]quinolin-3-one

35

Step A - Methyl Iodide

40

45



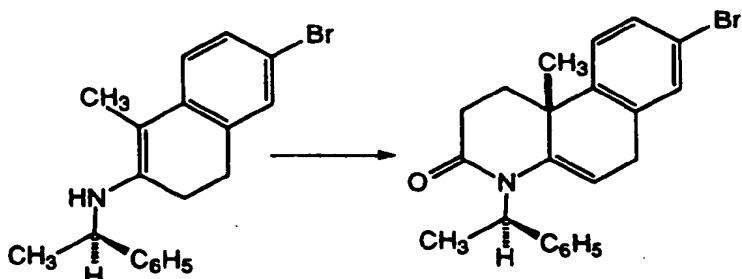
Methyl iodide (14.4 mL, 230 mmol, 1.15 equiv.) was added via syringe to the reaction mixture from Preparation 1 at -75 to -70° over 3 minutes. This solution was warmed to -5° in 20 minutes and then treated with methanesulfonic acid (24.8 g, 16.8 mL, 1.3 equiv.) affording a solution of the desired enamine admixed with diisopropylamine methanesulfonate as a slightly soluble, off-white precipitate, which was then removed by filtration.

Step B - Aza-Annulation

55

5

10

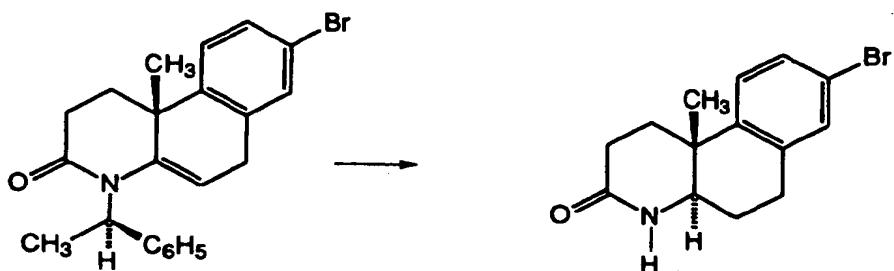


20

The reaction mixture solution from the above step was treated with acryloyl chloride (1.7 equiv.) at -75° in one portion over about 5 minutes. The mixture was then allowed to warm to -8° over 15 hours. The reaction was quenched by pouring into sodium bicarbonate (60 g in 240 mL of water at 5 to 7°, 15 minutes addition time, 20 minutes stir, pH should be basic). Dimethylaminopyridine (0.01 equiv, 2 mmol, 244 mg) was added and the mixture stirred another hour. The mixture was concentrated under vacuum (10-25°, initial volume 2000 mL; final volume 400 mL) and methylene chloride (400 mL) was added and the organic phase was washed with aqueous sulfuric acid (1.0 N, two 100 mL portions, pH 1-3) and sodium bicarbonate (1.0 N, 50 mL, pH 9). The organic extracts were dried and clarified by filtration over approximately 20 g of 4A molecular sieves. The mixture was concentrated under vacuum to a total weight of 129.6 g.

25

30



35

40

45

To about 103 g of the above residue were added 37 mL of triethylsilane and 46 mL of trifluoroacetic acid at 25°. After 1.5 hours reduction was approximately 50% complete. After an additional 12 hours the reduction was complete by TLC. The mixture was then refluxed for 2.5 hours. The mixture was allowed to cool and was concentrated *in vacuo* to approximately 25 g. The residue above was dissolved in 400 mL of methylene chloride, washed with aqueous sodium hydroxide (enough for pH 11), and concentrated under vacuum. This concentrate was then treated with diethyl ether (approximately 5 volumes at 22° then 0° for several hours). The mixture was filtered and rinsed with several small portions of ether affording the desired product after drying as a crystalline, white solid (yield = approximately 60% based on purity of bromotetralone).

Analysis by reverse phase high performance liquid chromatography on a Waters NOVA-PAK instrument, C-18 3.9 X 150 mm column, eluting with 2 mL/min. of 25% aqueous acetonitrile containing 1% ammonium acetate, operating the detector at 220 nm.

Potency: 91.2%

Related substances: 6.8%

50

Anal Calcd for C <sub>14</sub> H <sub>16</sub> NOBr:				
	C, 57.16;	H, 5.48;	N, 4.76;	Br, 27.16
Found:	C, 55.08;	H, 5.43;	N, 4.30;	Br, 27.78

55

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 21.60, 24.62, 28.24, 29.48, 33.15, 36.90, 57.28, 121.03, 127.42, 130.09, 132.86, 137.51,

143.26, 173.62

1H NMR (CDCl<sub>3</sub>): 1.18(s, 3H)

$\alpha$  589 nm - 90°

$\alpha$  365 nm - 302°

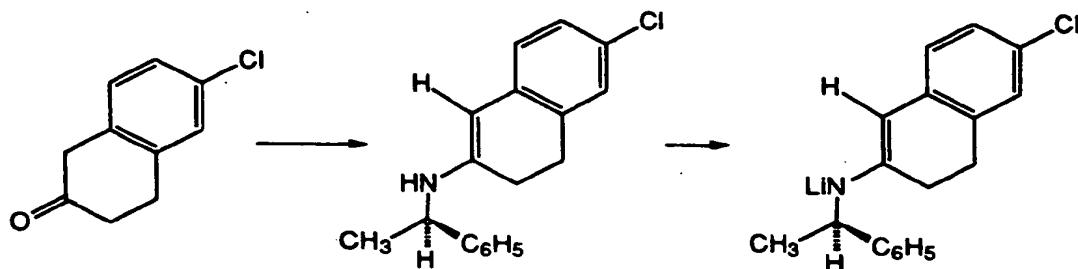
ee% > 98%, determined by chromatography on a Chiracel-OD instrument and 1 mL/min, 40°, eluting with 10% isopropanol in hexane and operating the detector at 220 nm.

Preparation 3 acrylic anhydride

Two hundred fifty ml of tetrahydrofuran was added to a 1 liter jacketed flask with stir bar and nitrogen purge, and 250 mg of butylated hydroxytoluene, 250 mg of hydroquinone and 25.3 g of triethylamine were added. The solution was cooled to 0°, and to it was added 18.0 g of acrylic acid over a 2 minute period. The solution was cooled again to 0°, and 22.6 g of acryloyl chloride was added over a 10 minute period. It is important to maintain the addition rate constant during the acryloyl chloride addition. Maintaining the jacket temperature at 0° and continuing the nitrogen purge, the solution was stirred for 1 hour, and then it was filtered in a vacuum filter and the cake was washed with 50 ml of additional tetrahydrofuran.

Preparation 4

(R)-6-chloro-2-(1-phenylethylamino)-3,4-dihydronaphthalene, lithium salt



6-Chloro-2-tetralone (4.51 g, 25 mmol) was reacted with 3.32 g of (R)-(+)-phenylethylamine and 20 mg of *p*-toluenesulfonic acid. The reaction was carried out as shown in Preparation 1 above in 100 mL of toluene, and when the reaction was complete the mixture was concentrated under vacuum and the residue was dissolved in 70 mL of tetrahydrofuran. The solution was cooled to -50 to -60°, and was added quickly to a solution of 1.15 equivalents of lithium diisopropylamide in 122 mL of tetrahydrofuran at -70 to -65°. The solution was allowed to warm to -20° for 20 minutes, and was then quickly recooled to -75°.

Preparation 5

(4aR)-(10bR)-8-chloro-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

40

45

50

55

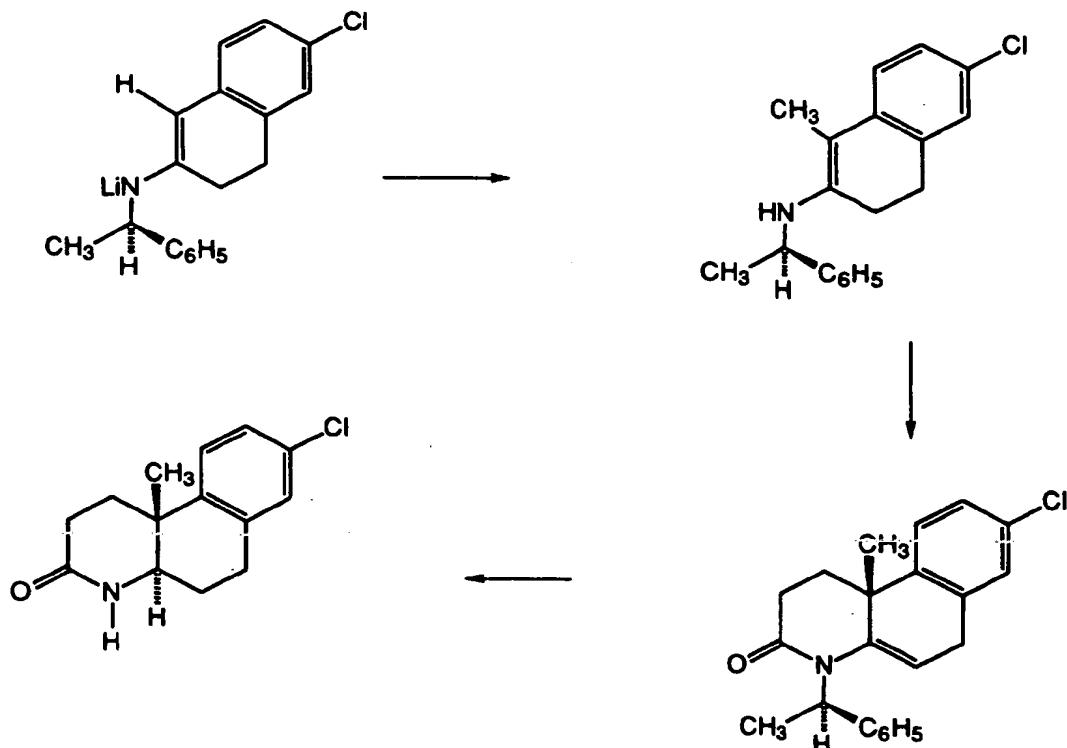
5

10

15

20

25



To the cold solution from Preparation 4, was added 1.15 equivalents of methyl iodide, and the mixture was allowed to warm to -5° over a 15 minute period with continued good stirring. Then 1.3 equiv. of methanesulfonic acid was added to the mixture over a 5 minute period.

That mixture was vigorously stirred for 10 minutes at -5°, and was then cooled again to -75°. To it was added in one portion, 2.4 equiv. of acrylic anhydride, with continued stirring, and the mixture was allowed to warm from -75° to -15° over a period of 13 hours.

The resulting reaction mixture was poured into a well stirred solution of aqueous sodium bicarbonate (2 g/200 mL at 20°) and 100 mg of dimethylaminopyridine. After two hours of stirring at ambient temperature, most of the volatiles were removed under vacuum, and 130 mL of methylene chloride was added. The mixture was washed with 50 mL of 1 N hydrochloric acid, and then with aqueous sodium bicarbonate, and the organic phase was dried and concentrated to a white foam (10.37 g).

The foam was placed in a flask in a ice bath and was treated with 40 mL triethylsilane and 60 mL of trifluoroacetic acid for 15 hours at 0° and was then held for four days at 25°. The volatiles were removed under vacuum, and the colorless oil was decanted from the solid product. The residue was dissolved in 200 mL of methylene chloride and washed with saturated aqueous sodium bicarbonate. The extracts were dried with 4A molecular sieves and evaporated. The residue was washed with 76 mL of diethyl ether to obtain 3.87 g of the desired product as a white solid admixed with a small amount of isomeric material.

MS = 249, 251 (M+, M+2)  
45 IR (CHCl<sub>3</sub>) = 3396, 1662 cm<sup>-1</sup>.

50

Anal Calcd for C <sub>14</sub> H <sub>16</sub> NOCl:				
Found:	C, 67.33;	H, 6.46;	N, 5.61;	Cl, 14.20
	C, 66.57;	H, 6.43;	N, 5.40;	Cl, 13.91

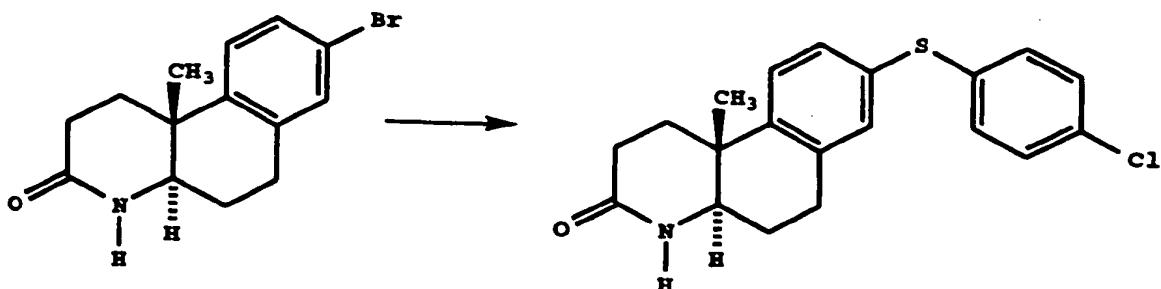
<sup>1</sup>H NMR (CDCl<sub>3</sub> 500 MHz): 1.16(s, 3H), 3.54(dxd, 1H), UV (MeOH):  $\lambda$ 205 (21000), 271(600), 280(600)

The following group of examples illustrates the preparation of compounds where X is a sulfur atom by reactions with disulfides.

55

#### Example 5

(+)-(4aR)-(10bR)-8-(4-chlorophenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



To a 3-necked 125 ml flask was added 50 ml of THF and 500 mg of (4aR)-(10bR)-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one at ambient temperature. The solution was cooled to -75°, and to it was added dropwise 1.7 ml of methylolithium in diethyl ether. The mixture was stirred for 15 minutes, and then 2.4 ml of t-butyllithium (1.7 M in pentane) was added and the temperature rose to -70°. The mixture was stirred for 5 minutes and then 1.95 g of bis(4-chlorophenyl)disulfide dissolved in 10 ml of THF was added in portions. The reaction mixture was stirred for 20 minutes at -75° and then was allowed to warm to ambient temperature. It was acidified with 1N hydrochloric acid, and was diluted with 300 ml of ethyl acetate. The organic solution was washed successively with 1N hydrochloric acid, 10% sodium carbonate solution, water and brine, and was then dried and concentrated under vacuum to obtain 2 g of a yellow oil. The oil was purified by chromatography over silica gel, eluting with a solvent beginning with 2% methanol in dichloromethane and going to 3% methanol/dichloromethane. The product-containing fractions were evaporated to obtain 540 mg of foam, which was crystallized from ethyl acetate to obtain 453 mg of purified product. mp 169°-172° FDMS: m/e=357.  $\alpha[D]_{589}=+83.91$ ,  $\alpha[D]_{365}=+293.47$  (methanol).

Analysis	Calculated	Found
C	67.12	67.33
H	5.63	5.82
N	3.91	3.78

The following examples were carried out according to the process of Example 5.

#### Example 6

(+)-(4aR)-(10bR)-8-(4-methylphenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 481 mg of the desired product. mp 209°-212° FDMS: m/e=337.  $\alpha[D]_{589}=+85.00$ ,  $\alpha[D]_{365}=+309.00$  (chloroform).

Analysis	Calculated	Found
C	74.74	75.00
H	6.87	6.94
N	4.15	4.10

#### Example 7

(+)-(4aR)-(10bR)-8-(2-chlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 790 mg of the desired product. mp 189°-191° FDMS: m/e=357.  $\alpha[D]_{589}=+80.66$ ,  $\alpha[D]_{365}=+281.3$  (chloroform).

Analysis	Calculated	Found
C	67.12	67.30
H	5.63	5.52
N	3.91	3.99

#### Example 8

(+)-(4aR)-(10bR)-8-(3-chlorophenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 810 mg of the desired product. mp 186°-187° FDMS: m/e=357.  $\alpha[D]_{589}=+80.5$ ,  $\alpha[D]_{365}=+292.6$  (chloroform).

Analysis	Calculated	Found
C	67.12	67.41
H	5.63	5.82
N	3.91	3.88

5

Example 9

10           (+)-(4aR)-(10bR)-8-(2-methylphenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 490 mg of the desired product. mp 192°, 196°-199° FDMS: m/e=337.  $\alpha[D]_{589} = +87.8$ ,  $\alpha[D]_{365} = +310.3$  (chloroform).

15

Analysis	Calculated	Found
C	74.74	74.46
H	6.87	6.90
N	4.15	3.90

20           Example 10

(+)-(4aR)-(10bR)-8-(3-methylphenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 480 mg of the desired product. mp 189°-191° FDMS: m/e=337.  $\alpha[D]_{589} = +87.8$ ,  $\alpha[D]_{365} = +316.5$  (chloroform).

25

Analysis	Calculated	Found
C	74.74	75.02
H	6.87	6.90
N	4.15	4.34

30

Example 11

(+)-(4aR)-(10bR)-8-(1-naphthylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 555 mg of the desired product. mp 199°-201° FDMS: m/e=373.  $\alpha[D]_{589} = +76.7$ ,  $\alpha[D]_{365} = +238.6$  (chloroform).

35

Analysis	Calculated	Found
C	77.18	76.96
H	6.21	6.12
N	3.75	3.64

40

Example 12

45           (+)-(4aR)-(10bR)-8-(2-methoxyphenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 580 mg of the desired product. mp 176°-179° FDMS: m/e=353.  $\alpha[D]_{589} = +80.4$ ,  $\alpha[D]_{365} = +287.9$  (chloroform).

50

Analysis	Calculated	Found
C	71.36	71.64
H	6.56	6.46
N	3.96	3.72

Example 13

55           (+)-(4aR)-(10bR)-8-(4-methoxyphenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 630 mg of the desired product. mp 194°-196° FDMS: m/e=353.  $\alpha[D]_{589} = +86.2$ ,  $\alpha[D]_{365} = +309.4$  (chloroform).

## EP 0 703 221 A1

Analysis	Calculated	Found
C	71.36	71.21
H	6.56	6.51
N	3.96	3.71

Example 14

(+)-(4aR)-(10bR)-8-(4-fluorophenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 600 mg of the desired product. mp 179°-181° FDMS: m/e=341.  $\alpha[D]_{589} = +88.9$ ,  $\alpha[D]_{365} = +313.2$  (chloroform).

Analysis	Calculated	Found
C	70.35	70.07
H	5.90	5.85
N	4.10	3.83

Example 15

(4aR)-(10bR)-8-(3-methoxyphenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 650 mg of the desired product. mp 154.5°-155.5° FDMS: m/e=353.

Analysis	Calculated	Found
C	71.36	71.29
H	6.56	6.56
N	3.96	3.91

Example 16

(+)-(4aR)-(10bR)-8-(3-fluorophenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 600 mg of the desired product. mp 154°-156° FDMS: m/e=341.  $\alpha[D]_{589} = +84.8$ ,  $\alpha[D]_{365} = +300.6$  (chloroform).

Analysis	Calculated	Found
C	70.35	70.38
H	5.90	5.96
N	4.10	4.09

Example 17

(+)-(4aR)-(10bR)-8-(2-fluorophenylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 640 mg of the desired product. mp 196°-198° FDMS: m/e=341.  $\alpha[D]_{589} = +84.2$ ,  $\alpha[D]_{365} = +300.8$  (chloroform).

Analysis	Calculated	Found
C	70.35	70.24
H	5.90	5.95
N	4.10	3.97

Example 18

(4aR)-(10bR)-8-(3-quinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 340 mg of the desired product. mp 168°-170° FDMS: m/e=374.

Analysis	Calculated	Found
C	73.76	73.56
H	5.92	5.96
N	7.48	7.36

5

Example 19

10 (4aR)-(10bR)-8-(2-quinolinythio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 560 mg of the desired product. mp 220°-222° FDMS: m/e=374.

15

Analysis	Calculated	Found
C	73.76	73.56
H	5.92	5.92
N	7.48	7.40

20

25 (+)-(4aR)-(10bR)-8-(8-quinolinythio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 375 mg of the desired product. mp >260° FDMS: m/e=374.  $\alpha[D]_{589} = +71.6$ ,  $\alpha[D]_{365} = \text{absorbance (chloroform)}$ .

25

Analysis	Calculated	Found
C	73.76	73.61
H	5.92	5.99
N	7.48	7.46

30

Example 21

(4aR)-(10bR)-8-(2-pyridinythio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 530 mg of the desired product. mp 223°-225° FDMS: m/e=324.

35

Analysis	Calculated	Found
C	70.34	70.09
H	6.21	6.24
N	8.63	8.57

40

Example 22

(4aR)-(10bR)-8-phenylthio-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 351 mg of the desired product. mp 183°-185° FDMS: m/e=323.

45

Analysis	Calculated	Found
C	74.27	73.99
H	6.54	6.68
N	4.33	4.53

50

Example 23

(4aR)-(10bR)-8-benzylthio-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 329 mg of the desired product. mp 172°-174° FDMS: m/e=337.  $\alpha[D]_{589} = 80.84$  (c=0.57 in chloroform).

Analysis	Calculated	Found
C	74.74	74.49
H	6.87	6.85
N	4.15	4.18

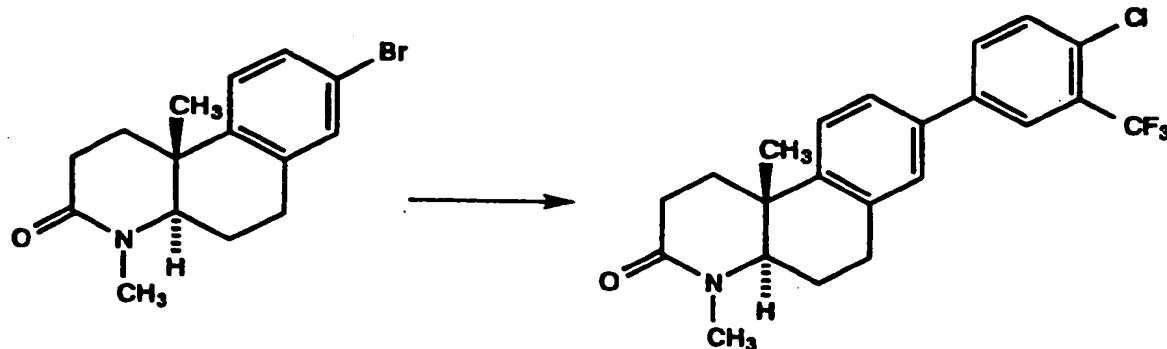
5

The following group of examples demonstrates syntheses in which a bromine-substituted benzoquinolinone nucleus

10 compound is reacted with a compound having a boronic acid leaving group and providing the R<sup>5</sup> group, where X is a

Example 24

15 (+)-(4aR)-(10bR)-4-methyl-8-(4-chloro-3-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



20

25

A 15 mL round bottom flask was charged with (+)-(4aR)-(10bR)-4-methyl-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (200 mg, 0.65 mmol), tetrakis(triphenylphosphine) palladium (0) (23 mg, 0.02 mmol), 4-chloro-3-trifluoromethylphenylboronic acid (175 mg, 0.78 mmol), 0.65 mL of 2 M aq. sodium carbonate solution and 2 mL of THF, fitted with a reflux condenser, and the stirred mixture was heated at 80°, under nitrogen, for 16 h. The mixture was cooled, diluted with chloroform (50 mL) and washed with brine (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (ethyl acetate eluent), to give 188 mg (71%) of the title compound as a white solid. mp 134-137°. FDMS: m/e = 407.  $\alpha$  [D]<sub>589</sub> = +59.74 (c = 1.02, chloroform).

40

analysis:	calculated	found
C	64.79	64.78
H	5.19	5.23
N	3.43	3.65

45

The following examples were carried out according to the process of Example 24.

50

Example 25

(+)-(4aR)-(10bR)-4-methyl-8-(3-chloro-4-hydroxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

55 Yield: 139 mg (61%) of the title compound as a white solid. mp 245°. FDMS: m/e = 355.  $\alpha$  [D]<sub>589</sub> = +17.62 (c = 1.02, chloroform).

analysis:	calculated	found
C	70.88	70.74
H	6.23	6.27
N	3.94	4.10

55

Example 26

(+)-(4aR)-(10bR)-4-methyl-8-(2,3-difluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

5 Yield: 111 mg (50%) of the title compound as a white solid. mp 147-148°. FDMS: m/e = 341  $\alpha[D]_{589} = +70.44$  (c=1.08, chloroform).

analysis:	calculated	found
C	73.88	73.79
H	6.20	6.27
N	4.10	4.16

Example 27

(+)-(4aR)-(10bR)-4-methyl-8-(3,4-difluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

15 Yield: 130 mg (58%) of the title compound as a white solid. mp 143-148°. FDMS: m/e = 341  $\alpha[D]_{589} = +65.12$  (c=0.97, chloroform).

analysis:	calculated	found
C	73.88	73.90
H	6.20	6.21
N	4.10	3.86

Example 28

(+)-(4aR)-(10bR)-4-methyl-8-(3-fluoro-4-hydroxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

20 Yield: 111 mg (50%) of the title compound as a white solid. mp >240°C. FDMS: m/e = 339.  $\alpha[D]_{589} = +11.21$  (c = 1.07, chloroform).

analysis:	calculated	found
C	74.31	74.12
H	6.53	6.53
N	4.13	3.88

Example 29

(+)-(4aR)-(10bR)-4-methyl-8-(3,4-ethylenedioxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

40 Yield: 189 mg (80%) of the title compound as an amorphous solid. mp 183-189°. FDMS: m/e = 363.  $\alpha[D]_{589} = +80.77$  (c = 1.04, chloroform).

analysis:	calculated	found
C	76.01	75.75
H	6.93	6.89
N	3.85	3.62

Example 30

(+)-(4aR)-(10bR)-4-methyl-8-(3,5-di[t-butyl]-4-hydroxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

50 Yield: 170 mg (58%) of the title compound as a white solid. mp >265°. FDMS: m/e = 433  $\alpha[D]_{589} = +46.45$  (c = 1.00, chloroform).

5

analysis:	calculated	found
C	80.33	78.52
H	9.06	9.01
N	3.23	2.69

Example 31

10 (+)-(4aR)-(10bR)-4-methyl-8-(2-trifluoromethyl-4-fluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 96 mg (38%) of the title compound as an amorphous foam. mp 70°. FDMS: m/e = 391.  $\alpha[D]_{589} = +55.81$  (c=0.60, chloroform).

15

analysis:	calculated	found
C	67.51	66.97
H	5.41	5.31
N	3.58	3.07

Example 32

20 (+)-(4aR)-(10bR)-4-methyl-8-(1-[4-t-butylcarbonylamino]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 239 mg (81%) of the title compound as an amorphous solid. mp >260°. FDMS: m/e = 454.  $\alpha[D]_{589} = +46.85$  (c = 0.51, chloroform).

25

analysis:	calculated	found
C	79.26	80.39
H	7.54	7.87
N	6.16	5.82

Example 33

30 (+)-(4aR)-(10bR)-4-methyl-8-(2-chloro-5-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 170 mg (64%) of the title compound as an oil. FDMS: m/e = 407.  $\alpha[D]_{589} = +49.42$  (c = 0.58, chloroform).

35

analysis:	calculated	found
C	64.79	65.65
H	5.19	5.39
N	3.43	3.75

Example 34

40 (+)-(4aR)-(10bR)-4-methyl-8-(3-t-butylcarboxamidophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 213 mg (81%) of the title compound as a waxy solid. FDMS: m/e = 404.  $\alpha[D]_{589} = +54.34$  (c = 0.45, chloroform).

45

analysis:	calculated	found
C	77.19	77.45
H	7.97	7.93
N	6.92	6.64

Example 35

(+)-(4aR)-(10bR)-4-methyl-8-(2-[1-diethylcarboxamido]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 240 mg (81%) of the title compound as a white solid. mp 208-211°. FDMS: m/e = 454.  $\alpha[D]_{589} = +49.37$  (c = 0.51, chloroform).

analysis:	calculated	found
C	79.26	77.29
H	7.54	7.57
N	6.16	6.11

Example 36

(+)-(4aR)-(10bR)-4-methyl-8-(4-hydroxy-3-methoxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 91 mg (40%) of the title compound as a white solid. mp 247-250°. FDMS: m/e = 351.  $\alpha[D]_{589} = +79.51$  (c = 0.75, chloroform).

analysis:	calculated	found
C	75.19	75.13
H	7.17	7.24
N	3.99	3.97

Example 37

(+)-(4aR)-(10bR)-4-methyl-8-(4-t-butylcarbonylaminophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20 Yield: 104 mg (40%) of the title compound as a brown solid. mp >265°C. FDMS: m/e = 404.  $\alpha[D]_{589} = +49.42$  (c = 0.56, chloroform).

analysis:	calculated	found
C	77.19	76.92
H	7.97	8.07
N	6.92	6.73

Example 38

(+)-(4aR)-(10bR)-4-methyl-8-(2-fluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

35 Yield: 172 mg (82%) of the title compound as a foam. mp 142-150°. FDMS: m/e = 323.  $\alpha[D]_{589} = +77.89$  (c=0.69, chloroform).

analysis:	calculated	found
C	77.99	78.09
H	6.86	6.95
N	4.33	4.30

Example 39

(+)-(4aR)-(10bR)-4-methyl-8-(2-methoxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

50 Yield: 160 mg (73%) of the title compound as a white solid. mp 152-156°. FDMS: m/e = 335.  $\alpha[D]_{589} = +77.45$  (c = 0.64, chloroform).

EP 0 703 221 A1

analysis:	calculated	found
C	78.77	78.53
H	7.51	7.25
N	4.18	4.35

5

Example 40

10 (+)-(4aR)-(10bR)-4-methyl-8-(2-methylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 146 mg (70%) of the title compound as an amorphous solid. mp 82-87°. FDMS: m/e =319.  $\alpha[D]_{589} = +63.96$  (c = 0.35, chloroform).

analysis:	calculated	found
C	82.72	82.63
H	7.89	7.95
N	4.38	4.10

15

20 Example 41

(+)-(4aR)-(10bR)-4-methyl-8-(2-chlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 186 mg (84 %) of the title compound as an amorphous foam. mp 111-120°. FDMS: m/e =339.  $\alpha[D]_{589} = +56.86$  (c = 0.64, chloroform).

25

analysis:	calculated	found
C	74.22	74.50
H	6.52	6.46
N	4.12	3.82

30

Example 42

35 (+)-(4aR)-(10bR)-4-methyl-8-(3,4-dimethoxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 171 mg (72 %) of the title compound as an amorphous foam. mp 108-112°. FDMS: m/e =365.  $\alpha[D]_{589} = +73.75$  (c = 0.56, chloroform).

40

analysis:	calculated	found
C	75.59	75.88
H	7.45	7.57
N	3.83	3.85

45 Example 43

(+)-(4aR)-(10bR)-4-methyl-8-(2-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 201 mg (83 %) of the title compound as an oil. FDMS: m/e =373.  $\alpha[D]_{589} = +60.00$  (c = 0.36, chloroform).

50

analysis:	calculated	found
C	70.76	70.55
H	5.94	7.97
N	3.75	3.49

55 Example 44

(+)-(4aR)-(10bR)-4-methyl-8-(3-fluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 177 mg (84 %) of the title compound as an amorphous foam. mp 116-120°. FDMS: m/e =323.  $\alpha[D]_{589} = +81.84$

(c = 0.47, chloroform).

analysis:	calculated	found
C	77.99	77.69
H	6.86	6.85
N	4.33	4.11

Example 45

(+)-(4aR)-(10bR)-8-(3-quinoliny)-10b-methyl-1,2,3,4,4a,-5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 141 mg (63%) of the title compound as a white solid. mp 265-266°. FDMS: m/e = 342.  $\alpha[D]_{589} = +88.70$  (c = 0.84, chloroform).

Example 46

(+)-(4aR)-(10bR)-4-methyl-8-(4-fluoro-3-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 110 mg (43%) of the title compound as an amorphous foam. FDMS: m/e = 323.  $\alpha[D]_{589} = +51.47$  (c = 0.52, chloroform).

analysis:	calculated	found
C	67.51	67.80
H	5.41	5.46
N	3.58	3.32

Example 47

(+)-(4aR)-(10bR)-4-methyl-8-(4-methoxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 173 mg (79%) of the title compound as a white solid. mp 150°. FDMS: m/e = 335.  $\alpha[D]_{589} = +73.82$  (c=1.01, methanol).

analysis:	calculated	found
C	78.77	78.49
H	7.51	7.44
N	4.18	4.43

Example 48

(+)-(4aR)-(10bR)-4-methyl-8-(3-methoxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 144 mg (66%) of the title compound as a white solid. mp 140°. FDMS: m/e = 335.  $\alpha[D]_{589} = +77.45$  (c=1.02, chloroform).

analysis:	calculated	found
C	78.77	78.53
H	7.51	7.50
N	4.18	3.92

Example 49

(+)-(4aR)-(10bR)-4-methyl-8-phenyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 139 mg (70%) of the title compound as a white solid. mp 155°. FDMS: m/e = 305.

EP 0 703 221 A1

analysis:	calculated	found
C	82.59	82.79
H	7.59	7.59
N	4.59	4.39

5

Example 50

10 (+)-(4aR)-(10bR)-4-methyl-8-(4-chlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 166 mg (75%) of the title compound as a white solid. mp 192°. FDMS: m/e = 339.  $\alpha[D]_{589} = +76.14$  (c = 1.00, chloroform).

analysis:	calculated	found
C	74.22	74.17
H	6.52	6.68
N	4.12	3.97

15 Example 51

(+)-(4aR)-(10bR)-4-methyl-8-(4-methylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 150 mg (72%) of the title compound as a white solid. mp 178°. FDMS: m/e = 319.  $\alpha[D]_{589} = +77.14$  (c=1.00, chloroform).

analysis:	calculated	found
C	82.72	82.66
H	7.89	7.95
N	4.38	4.20

25

30

Example 52

(+)-(4aR)-(10bR)-4-methyl-8-(3,5-dichlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
35 Yield: 145 mg (60%) of the title compound as a white solid. mp 172°. FDMS: m/e = 374  $\alpha[D]_{589} = +70.91$  (c=0.55, chloroform).

analysis:	calculated	found
C	67.39	67.43
H	5.65	5.67
N	3.74	3.65

40

Example 53

45

(+)-(4aR)-(10bR)-4-methyl-8-(1-naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 116 mg (50%) of the title compound as a white solid. mp 159°. FDMS: m/e = 355.  $\alpha[D]_{589} = +60.00$  (c=0.50, chloroform).

analysis:	calculated	found
C	84.47	84.73
H	7.09	7.08
N	3.94	3.89

50

55

Example 54

(+)-(4aR)-(10bR)-4-methyl-8-(3-pyridyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 112 mg (56%) of the title compound as a white solid. mp 135°. FDMS: m/e = 306.

analysis:	calculated	found
C	78.40	78.37
H	7.24	7.37
N	9.14	9.14

Example 55

(+)-(4aR)-(10bR)-4-methyl-8-(3-biphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 176 mg (71%) of the title compound as a white solid. mp 131°. FDMS: m/e = 381.  $\alpha[D]_{589} = +71.15$  (c = 0.52,  $\text{CHCl}_3$ ).

analysis:	calculated	found
C	85.00	84.77
H	7.13	7.31
N	3.67	3.46

Example 56

(+)-(4aR)-(10bR)-4-methyl-8-(4-phenoxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 206 mg (80%) of the title compound as a white solid. mp 148-150°. FDMS: m/e = 397.  $\alpha[D]_{589} = +64.51$  (c = 0.62, chloroform).

analysis:	calculated	found
C	81.58	81.47
H	6.85	8.83
N	3.52	3.60

Example 57

(+)-(4aR)-(10bR)-4-methyl-8-(3-formylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 141 mg (65%) of the title compound as a white solid. mp 163°. FDMS: m/e = 333.

analysis:	calculated	found
C	79.25	79.16
H	6.95	6.99
N	4.20	3.92

Example 58

(+)-(4aR)-(10bR)-4-methyl-8-(3-formyl-4-hydroxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 85 mg (37%) of the title compound as a white solid. mp 184-187°. FDMS: m/e = 349.

analysis:	calculated	found
C	75.62	75.86
H	6.63	6.72
N	4.01	3.87

Example 59

(+)-(4aR)-(10bR)-4-methyl-8-(4-dimethylaminophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

lin-3-one

Yield: 119 mg (53%) of the title compound as an amorphous foam. mp 197-202°. FDMS: m/e = 348.  $\alpha[D]_{589} = +76.84$  (c=0.95, chloroform).

analysis:	calculated	found
C	78.27	77.92
H	8.10	8.12
N	8.04	7.84

Example 60

(+)-(4aR)-(10bR)-4-methyl-8-(2-[6-hydroxy]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 47 mg (20%) of the title compound as a white solid. mp >260° (decomp.) FDMS: m/e = 371.

analysis:	calculated	found
C	80.83	79.84
H	6.78	6.73
N	3.77	3.25

Example 61

(+)-(4aR)-(10bR)-4-methyl-8-(9-anthracenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 112 mg (43%) of the title compound as an amorphous solid. mp 95-110°. FDMS: m/e = 405.  $\alpha[D]_{589} = +45.73$  (c=0.66, chloroform).

analysis:	calculated	found
C	85.89	84.93
H	6.71	6.55
N	3.45	3.01

Example 62

(+)-(4aR)-(10bR)-4-methyl-8-(2-[6-benzyloxy]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 73 mg (24%) of the title compound as a white solid. mp 173-176° FDMS: m/e = 361.  $\alpha[D]_{589} = +66.07$  (c = 0.56, chloroform).

analysis:	calculated	found
C	83.26	83.50
H	6.77	6.84
N	3.03	3.03

Example 63

(+)-(4aR)-(10bR)-4-methyl-8-(3-chlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 164 mg (74%) of the title compound as an amorphous foam. mp 158-65°. FDMS: m/e = 339.  $\alpha[D]_{589} = +74.90$  (c = 1.00, methanol).

analysis:	calculated	found
C	74.22	73.95
H	6.52	6.51
N	4.12	4.89

Example 64

(+)-(4aR)-(10bR)-4-methyl-8-(1-[4-fluoro]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 188 mg (77%) of the title compound as an amorphous foam. mp 115-125°. FDMS: m/e = 373.  $\alpha[D]_{589} = +60.78$   
 (c=1.02, chloroform).

analysis:	calculated	found
C	80.40	78.80
H	6.48	6.35
N	3.75	3.41

Example 65

(+)-(4aR)-(10bR)-4-methyl-8-(1-[4-methyl]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 36 mg (15%) of the title compound as a white solid. mp 175-178°. FDMS: m/e = 369.  $\alpha[D]_{589} = +63.81$  (c=1.05, chloroform).

analysis:	calculated	found
C	84.51	84.73
H	7.36	7.44
N	3.79	3.54

Example 66

(+)-(4aR)-(10bR)-4-methyl-8-(5-acenaphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 170 mg (69%) of the title compound as a white solid. mp > 200° (decomp.) FDMS: m/e = 381  $\alpha[D]_{589} = +61.47$  (c=0.84, chloroform).

analysis:	calculated	found
C	85.00	85.24
H	7.13	7.17
N	3.67	3.51

Example 67

(+)-(4aR)-(10bR)-4-methyl-8-(9-phenanthrenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 80 mg (30%) of the title compound as a white solid. mp 218-220°. FDMS: m/e = 405.  $\alpha[D]_{589} = +63.01$  (c=0.98, chloroform).

analysis:	calculated	found
C	85.89	86.06
H	6.71	6.83
N	3.45	3.39

Example 68

(+)-(4aR)-(10bR)-4-methyl-8-(4-[N-propyl,N-cyclopropyl-methylamino]-1-naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 193 mg (64%) of the title compound as an oil. FDMS: m/e = 466.  $\alpha[D]_{589} = +50.52$  (c=0.95, chloroform).

Example 69

(+)-(4aR)-(10bR)-4-methyl-8-(2,3-dimethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 55 mg (25 %) of the title compound as an amorphous solid. mp 133-140°. FDMS: m/e = 333.  $\alpha[D]_{589} = +61.90$

(c = 1.05, methanol).

analysis:	calculated	found
C	82.84	82.64
H	8.16	8.07
N	4.20	4.15

Example 70

(+)-(4aR)-(10bR)-4-methyl-8-(3,4-methylenedioxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 130 mg (57%) of the title compound as an amorphous solid. mp 146-152°. FDMS: m/e = 349.  $\alpha[D]_{589} = +67.92$  (c = 1.06, chloroform).

analysis:	calculated	found
C	75.62	75.46
H	6.63	6.77
N	4.01	3.80

Example 71

(+)-(4aR)-(10bR)-4-methyl-8-(2-naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 126 mg (55%) of the title compound as a white solid. mp 221-223°. FDMS: m/e = 355.  $\alpha[D]_{589} = +73.58$  (c = 1.06, chloroform).

analysis:	calculated	found
C	84.47	84.63
H	7.09	7.06
N	3.94	3.93

Example 72

(+)-(4aR)-(10bR)-4-methyl-8-(1-[2-methyl]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 104 mg (44%) of the title compound as a white solid. mp 196-200°. FDMS: m/e = 369.  $\alpha[D]_{589} = +54.72$  (c = 1.06, chloroform).

analysis:	calculated	found
C	84.51	84.27
H	7.36	7.42
N	3.79	3.93

Example 73

(+)-(4aR)-(10bR)-4-methyl-8-(2,3-dichlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 193 mg (79%) of the title compound as an off-white solid. mp 131-134°. FDMS: m/e = 373  $\alpha[D]_{589} = +81.02$  (c = 1.05, chloroform).

analysis:	calculated	found
C	67.39	68.46
H	5.65	5.70
N	3.74	3.75

Example 74

(+)-(4aR)-(10bR)-4-methyl-8-(2-[N,N-diethylcarboxamido]phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 180 mg (68%) of the title compound as a white solid. mp 147-149°. FDMS: m/e = 404  $\alpha[D]_{589} = +56.86$  (c = 1.02, chloroform).

analysis:	calculated	found
C	77.19	76.99
H	7.97	8.05
N	6.92	6.87

Example 75

(+)-(4aR)-(10bR)-4-methyl-8-(4-t-butylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 163 mg (69%) of the title compound as an amorphous solid. mp 141-147°. FDMS: m/e = 361  $\alpha[D]_{589} = +67.88$  (c = 1.05, chloroform).

analysis:	calculated	found
C	83.06	83.34
H	8.64	8.72
N	3.87	3.76

Example 76

(+)-(4aR)-(10bR)-4-methyl-8-(4-n-butylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 180 mg (77%) of the title compound as a white solid. mp 102-108°. FDMS: m/e = 361.  $\alpha[D]_{589} = +68.70$  (c = 1.05, chloroform).

analysis:	calculated	found
C	83.06	82.98
H	8.64	8.73
N	3.87	3.64

Example 77

40 (+)-(4aR)-(10bR)-4-methyl-8-(3,4-dichlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 156mg (64%) of the title compound as a foam. mp 129-135°. FDMS: m/e = 374.  $\alpha[D]_{589} = +68.66$  (c=1.03, chloroform).

analysis:	calculated	found
C	67.39	68.37
H	5.65	5.81
N	3.74	3.63

Example 78

(+)-(4aR)-(10bR)-4-methyl-8-(4-trifluoromethoxyphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

55 Yield: 137 mg (56%) of the title compound as a waxy solid. FDMS: m/e = 389.  $\alpha[D]_{589} = +48.95$  (c = 0.96, chloroform).

Example 79

(+)-(4aR)-(10bR)-4-methyl-8-(4-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

EP 0 703 221 A1

Yield: 137 mg (56%) of the title compound as a white solid. mp 86-89°. FDMS: m/e = 373  $\alpha[D]_{589} = +28.90$  (c = 1.04, chloroform).

analysis:	calculated	found
C	70.76	70.96
H	5.94	6.00
N	3.75	3.09

10 Example 80

(+)-(4aR)-(10bR)-4-methyl-8-(3-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 180 mg (77%) of the title compound as an amorphous foam. mp 64-87°. FDMS: m/e = 373.  $\alpha[D]_{589} = +64.42$  (c=1.04, chloroform).

analysis:	calculated	found
C	70.76	71.04
H	5.94	5.98
N	3.75	3.48

20 Example 81

(+)-(4aR)-(10bR)-4-methyl-8-(2-[6-methoxy]naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 233 mg (93%) of the title compound as a white solid. mp 216-221°. FDMS: m/e = 385.  $\alpha[D]_{589} = +59.64$  (c=0.97, chloroform).

analysis:	calculated	found
C	81.01	80.72
H	7.06	6.99
N	3.63	3.57

35 Example 82

(+)-(4aR)-(10bR)-4-methyl-8-(2-benzothienyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 190 mg (81%) of the title compound as a white solid. mp 247-250°. FDMS: m/e = 361.  $\alpha[D]_{589} = +93.33$  (c=0.36, chloroform).

analysis:	calculated	found
C	76.42	76.29
H	6.41	6.37
N	3.87	3.68

45 Example 83

(+)-(4aR)-(10bR)-4-methyl-8-(3,5-dimethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 186 mg (86 %) of the title compound as a white solid. mp 129-130°. FDMS: m/e = 333.  $\alpha[D]_{589} = +73.31$  (c = 1.00, chloroform).

analysis:	calculated	found
C	82.84	82.59
H	8.16	8.08
N	4.20	4.01

Example 84

(+-)(4aR)-(10bR)-4-methyl-8-(4-biphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 178 mg (72 %) of the title compound as a white solid. mp 206-207°. FDMS: m/e =381.  $\alpha[D]_{589} = +63.93$  (c = 1.01, chloroform).

5

10

analysis:	calculated	found
C	85.00	84.51
H	7.13	6.85
N	3.67	3.37

Example 85

(+-)(4aR)-(10bR)-4-methyl-8-(4-fluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 140 mg (67 %) of the title compound as a white solid. mp 121-122°. FDMS: m/e =323.  $\alpha[D]_{589} = +79.46$  (c = 0.99, chloroform).

20

analysis:	calculated	found
C	77.99	77.70
H	6.86	6.85
N	4.33	4.25

25

Example 86

(+-)(4aR)-(10bR)-4-methyl-8-(3-nitrophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 159 mg (70 %) of the title compound as a tan solid. mp 181-183°. FDMS: m/e =350.  $\alpha[D]_{589} = +80.70$  (c = 1.04, chloroform).

30

analysis:	calculated	found
C	71.98	71.85
H	6.33	6.22
N	7.99	7.71

35

Example 87

(+-)(4aR)-(10bR)-4-methyl-8-(3,5-bis[trifluoromethyl]phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

40

Yield: 194 mg (68 %) of the title compound as a white solid. mp 110-112°. FDMS: m/e =441  $\alpha[D]_{589} = +80.70$  (c = 1.05, methanol).

45

analysis:	calculated	found
C	62.58	62.43
H	4.79	4.81
N	3.17	3.40

50

Example 88

(+-)(4aR)-(10bR)-4-methyl-8-(3-chloro-4-fluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

55

Yield: 170 mg (73%) of the title compound as a white solid. mp 114-116°. FDMS: m/e =357.  $\alpha[D]_{589} = +86.00$  (c = 1.00, methanol).

## EP 0 703 221 A1

5

analysis:	calculated	found
C	70.48	70.35
H	5.91	6.00
N	3.91	3.95

Example 89

10 (+)-(4aR)-(10bR)-4-methyl-8-(4-[4-ethoxybiphenyl]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 166 mg (60%) of the title compound as a white solid. mp 177-179°. FDMS: m/e = 425.  $\alpha[D]_{589} = +66.30$  (c = 1.03, chloroform).

15

analysis	calculated	found
C	81.85	81.64
H	7.34	7.12
N	3.29	3.57

Example 90

20 (+)-(4aR)-(10bR)-4-methyl-8-(3-aminophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 170 mg (82%) of the title compound as a tan solid. mp 230-231° (decomp.) FDMS: m/e = 320.  $\alpha[D]_{589} = +80.00$  (c = 1.05, methanol).

25

analysis	calculated	found
C	78.71	78.99
H	7.55	7.55
N	8.74	9.12

Example 91

30 (+)-(4aR)-(10bR)-4-methyl-8-[3-([5-dimethylamino-1-naphthyl]sulfonylamino)phenyl]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 94 mg (63%) of the title compound as a yellow solid. mp 130-140° (decomp.) FDMS: m/e = 553.  $\alpha[D]_{589} = +3.01$  (c = 1.03 methanol).

Example 92

40 (+)-(4aR)-(10bR)-8-(1-naphthyl)-10b-methyl-1,2,3,4,4a,-5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 405 mg (70%) of the title compound as a white solid. mp 247-248°. FDMS: m/e = 341.  $\alpha[D]_{589} = +1.93$  (c = 1.04, methanol).

Example 93

45 (+)-(4aR)-(10bR)-8-(3-nitrophenyl)-10b-methyl-1,2,3,4,4a,-5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 456 mg (80%) of the title compound as a white solid. mp 223-225°. FDMS: m/e = 336.  $\alpha[D]_{589} = +45.63$  (c = 1.03, methanol).

Example 94

50 (+)-(4aR)-(10bR)-4-methyl-8-(2,4-dichlorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 157 mg (65%) of the title compound as an amorphous foam. mp 45-48°. FDMS: m/e = 374.

analysis	calculated	found
C	67.39	66.95
H	5.65	5.43
N	3.74	3.82

5

The following group of examples illustrate alkylations, other than the preferred alkylations of Examples 1-4 above, which provide modifications of the benzoquinolinone nucleus.

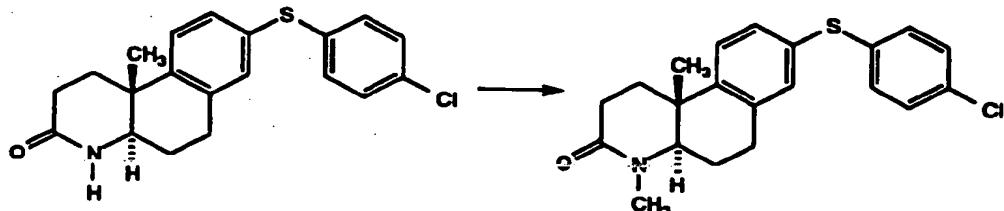
10

Example 95

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(4-chlorophenylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15

20



25

30

A 350 mg portion of (4aR)-(10bR)-10b-methyl-8-(4-chlorophenylthio)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was slurried in 14 ml of t-butanol in a nitrogen-blanketed flask, and 0.2 ml of a 25 mg/ml aqueous solution of methyl iodide was added, followed by 330 mg of potassium t-butoxide. The mixture was stirred at ambient temperature for 5 hours, and then the reaction mixture was poured into water, and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with water and with brine, dried over sodium sulfate and concentrated under vacuum to obtain an oil, which was purified by silica gel chromatography on a Chromatotron (Harrison Research Co.), using dichloromethane containing from 1% to 3% of methanol as the eluent. The product-containing fractions were combined and concentrated under vacuum to obtain 330 mg of solid, which was crystallized from heptane/ethyl acetate to obtain 254 mg of the desired product. mp 122°-124° FDMS: m/e=371.  $\alpha[D]_{589} = +60.2$ ,  $\alpha[D]_{365} = +262.55$  (chloroform).

35

Analysis	Calculated	Found
C	67.82	68.05
H	5.96	6.00
N	3.77	3.89

40

The following examples were carried out according to the process of Example 95.

45

Example 96

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(4-methylphenylthio)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 280 mg of the desired product. mp 154°-156° FDMS: m/e=351.  $\alpha[D]_{589} = +76.6$ ,  $\alpha[D]_{365} = +282.53$  (chloroform).

50

Analysis	Calculated	Found
C	75.17	74.95
H	7.17	7.25
N	3.99	4.17

55

Example 97

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(phenylsulfonyl)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 144 mg of the desired product. mp 165°-167° FDMS: m/e=369.  $\alpha[D]_{589} = +76.2$ ,  $\alpha[D]_{365} = +269.7$  (chloroform).

EP 0 703 221 A1

Analysis	Calculated	Found
C	68.27	68.44
H	6.27	6.39
N	3.79	3.69

5

Example 98

10 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-naphthylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 137 mg of the desired product. mp 138°-139.5° FDMS: m/e=387.  $\alpha[D]_{589} = +69.6$ ,  $\alpha[D]_{365} = +261.4$  (chloroform).

15

Analysis	Calculated	Found
C	77.48	77.28
H	6.50	6.63
N	3.61	3.71

20

Example 99

25 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-chlorophenylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 420 mg of the desired product. mp 123°-125° FDMS: m/e=371.  $\alpha[D]_{589} = +76.0$ ,  $\alpha[D]_{365} = +255.3$  (chloroform).

25

Analysis	Calculated	Found
C	67.82	67.87
H	5.96	5.97
N	3.77	3.94

30

Example 100

35 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(3-chlorophenylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 525 mg. FDMS: m/e=371.  $\alpha[D]_{589} = +72.9$ ,  $\alpha[D]_{365} = +265.2$  (chloroform).

35

Analysis	Calculated	Found
C	67.82	67.60
H	5.96	5.91
N	3.77	3.86

40

Example 101

45 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-methylphenylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 330 mg of the desired product. mp 105°-106° FDMS: m/e=351.  $\alpha[D]_{589} = +77.0$ ,  $\alpha[D]_{365} = +282.8$  (chloroform).

45

Analysis	Calculated	Found
C	75.17	75.46
H	7.17	7.34
N	3.98	3.95

50

Example 102

55 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(3-methylphenylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 290 mg of the desired product. mp 103°-104° FDMS: m/e=351.  $\alpha[D]_{589} = +80.3$ ,  $\alpha[D]_{365} = +292.2$  (chloroform).

Analysis	Calculated	Found
C	75.17	75.40
H	7.17	7.19
N	3.98	3.98

5

Example 103

10 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(1-naphthylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 300 mg of the desired product. mp 161°-162° FDMS: m/e=387.  $\alpha[D]_{589} = +65.2$ ,  $\alpha[D]_{365} = +248.4$  (chloroform).

Analysis	Calculated	Found
C	77.48	77.64
H	6.50	6.54
N	3.61	3.54

15

Example 104

20

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-methoxyphenylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 300 mg of the desired product. mp 166°-167.5° FDMS: m/e=367.  $\alpha[D]_{589} = +72.7$ ,  $\alpha[D]_{365} = +265.1$  (chloroform).

Analysis	Calculated	Found
C	71.90	71.98
H	6.86	6.64
N	3.81	3.67

25

30

Example 105

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(4-methoxyphenylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 400 mg of the desired product. mp 150°-151° FDMS: m/e=367.  $\alpha[D]_{589} = +74.1$ ,  $\alpha[D]_{365} = +276.8$  (chloroform).

35

Analysis	Calculated	Found
C	71.90	71.95
H	6.86	6.64
N	3.81	3.85

40

Example 106

(4aR)-(10bR)-4,10b-dimethyl-8-(3-quinolinylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 255 mg of the desired product, as an amorphous solid. FDMS: m/e=388.

45

Analysis	Calculated	Found
C	74.19	73.94
H	6.23	6.41
N	7.21	7.13

50

Example 107

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-quinolinylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

55 Yield: 300 mg of the desired product. mp 175°-177° FDMS: m/e=388.  $\alpha[D]_{589} = +65.9$ ,  $\alpha[D]_{365} = \text{absorbance}$  (chloroform).

EP 0 703 221 A1

Analysis	Calculated	Found
C	74.19	74.01
H	6.23	6.10
N	7.21	7.39

5

Example 108

10 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-fluorophenylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 490 mg of the desired product, which was not crystalline. mp 100°-103° FDMS: m/e=354.  $\alpha[D]_{589} = +76.5$ ,  $\alpha[D]_{365} = +273.6$  (chloroform).

Analysis	Calculated	Found
C	70.96	71.21
H	6.24	6.32
N	3.94	4.16

15

Example 109

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(3-fluorophenylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 430 mg of the desired product in the form of an oil. FDMS: m/e=355.  $\alpha[D]_{589} = +76.5$ ,  $\alpha[D]_{365} = +275.2$  (chloroform).

Analysis	Calculated	Found
C	70.96	71.11
H	6.24	6.32
N	3.94	3.98

20

Example 110

(4aR)-(10bR)-4,10b-dimethyl-8-(8-quinolinylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 114 mg of the desired product. mp 241°-242° FDMS: m/e=388.

Analysis	Calculated	Found
C	74.19	73.98
H	6.23	6.15
N	7.21	7.18

25

Example 111

40 (+)-(4aR)-(10bR)-4,10b-dimethyl-8-(2-pyridinylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 330 mg of the desired product. mp 174°-176° FDMS: m/e=338.  $\alpha[D]_{589} = +79.8$ ,  $\alpha[D]_{365} = +288.7$  (chloroform).

Analysis	Calculated	Found
C	70.97	70.70
H	6.55	6.74
N	8.28	8.06

45

Example 112

55 (4aR)-(10bR)-4,10b-dimethyl-8-(2-benzothiazolylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 84 mg of the desired product. mp 188°-189° FDMS: m/e=394.

Analysis	Calculated	Found
C	66.97	66.73
H	5.62	5.65
N	7.10	6.87

5

Example 113

10 (4aR)-(10bR)-4,10b-dimethyl-8-(1-isoquinolinylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 90 mg of the desired product. mp 196°-199° FDMS: m/e=388.

Analysis	Calculated	Found
C	74.19	74.08
H	6.23	6.41
N	7.21	7.45

15

Example 114

20 (4aR)-(10bR)-4,10b-dimethyl-8-(4-isoquinolinylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 140 mg of the desired product. mp 161°-163° FDMS: m/e=388.

Analysis	Calculated	Found
C	74.19	74.05
H	6.23	6.18
N	7.21	7.47

25

Example 115

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(4-pyridinylthio)-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 228 mg of the desired product. mp 157°-158° FDMS: m/e=338.  $\alpha[D]_{589} = +77.5$ ,  $\alpha[D]_{365} = \text{absorbance (chloroform)}$ .

35

Analysis	Calculated	Found
C	70.97	71.25
H	6.55	6.27
N	8.28	8.27

40

Example 116

(4aR)-(10bR)-4,10b-dimethyl-8-phenylthio-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
45 Yield: 0.90 g of white crystals: mp 109-112°; FD MS 337 M+; Calcd for  $C_{21}H_{23}N_1O_1S_1$ .

Analysis	Calculated	Found
C	74.74	74.55
H	6.87	6.79
N	4.15	4.35

50

Example 117

55 (+)-(4aR)-(10bR)-4-methyl-8-(1-naphthyl)-10b-methyl-3,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one  
Yield: 16 mg (70%) of the title compound as a yellow solid, upon trituration from diethyl ether/hexanes. mp 172-173°.  
FDMS: m/e = 353.

5

analysis:	calculated	found
C	84.92	84.70
H	6.56	6.29
N	3.96	3.55

Example 118

10 (+)-(4aR)-(10bR)-4-methyl-8-(3-nitrophenyl)-10b-methyl-3,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one  
 Yield: 9 mg (75%) of the title compound as a white solid, upon trituration from diethyl ether/hexanes. mp 175-177°.  
 FDMS: m/e = 348.

Example 119

15 (+)-(4aR)-(10bR)-4-methyl-8-(4-nitrophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 10 mg (70%) of the title compound as a white solid. mp 59-60°. FDMS: m/e = 350.

Example 120

20 (+)-(4aR)-(10bR)-4-methyl-8-(4-methylthiophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 15 mg (72%) of the title compound as a white solid. mp 115-117°. FDMS: m/e = 351.

Example 121

25 (+)-(4aR)-(10bR)-4-methyl-8-(4-cyanophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 20 mg (80%) of the title compound as a white solid. mp 148-150°. FDMS: m/e = 330.

30

analysis:	calculated	found
C	79.97	79.77
H	6.71	6.63
N	8.48	8.69

Example 122

35 (+)-(4aR)-(10bR)-4-methyl-8-(4-[isopropylcarbonyl]phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 20 mg (54 %) of the title compound as a white solid. mp 101-103°. FDMS: m/e = 375.

Example 123

40 (+)-(4aR)-(10bR)-4-methyl-8-(4-methylsulfonamidophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 20 mg (56%) of the title compound as an oil. FDMS: m/e = 398.

Example 124

45 (+)-(4aR)-(10bR)-4-methyl-8-(2-nitrophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 50 mg (80 %) of the title compound as a white solid. mp 130-131°. FDMS: m/e = 350.

Example 125

50 (+)-(4aR)-(10bR)-4-methyl-8-(2-cyanophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 50 mg (87 %) of the title compound as a white solid. mp 54-55°. FDMS: m/e = 330.  $\alpha_{D}^{25} = +74.33$  (c = 0.36, chloroform).

Example 126

(+)-(4aR)-(10bR)-4-methyl-8-(2-[5-(phenoxyethyl)thienyl])-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 65 mg (90 %) of the title compound as a white solid. mp 149-151°. FDMS: m/e = 417  $\alpha[D]_{589} = +68.50$  (c = 0.89, chloroform).

Example 127

10 (+)-(4aR)-(10bR)-4-methyl-8-(2-methylthiophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 15 mg (26 %) of the title compound as an oil. FDMS: m/e = 351.

Example 128

15 (+)-(4aR)-(10bR)-4-methyl-8-(2,4,5-trifluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 40 mg (89%) of the title compound as a foam. FDMS: m/e = 359.

Example 129

20 (+)-(4aR)-(10bR)-4-methyl-8-(2-[5-(4-fluorophenoxy-methyl)thienyl])-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 35 mg (71 %) of the title compound as a white solid. mp 136-138°. FDMS: m/e = 435  $\alpha[D]_{589} = +63.40$  (c = 0.74, chloroform).

25 Example 130

(+)-(4aR)-(10bR)-4-methyl-8-(2,3,5-trifluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 30 mg (83%) of the title compound as a foam. FDMS: m/e = 359.

30 Example 131

(+)-(4aR)-(10bR)-4-methyl-8-(2-fluorenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 26 mg (82%) of the title compound as an off-white solid. mp 175° (decomp). FDMS: m/e = 393.

35 Example 132

(+)-(4aR)-(10bR)-4-methyl-8-(3-[2,5-dichlororo]thienyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

40 Yield: 35 mg (69%) of the title compound as an oil. FDMS: m/e = 379.

Example 133

(+)-(4aR)-(10bR)-4-methyl-8-(4-nitro-2-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

45 Yield: 35 mg (70%) of the title compound as a white solid. mp 128-130°. FDMS: m/e = 418.

Example 134

(+)-(4aR)-(10bR)-4-methyl-8-(2-nitro-4-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

50 Yield: 38 mg (76%) of the title compound as an off-white solid. mp 55-57°. FDMS: m/e = 418.  $\alpha[D]_{589} = +60.50$  (c = 0.16, methanol).

Example 135

(+)-(4aR)-(10bR)-4-methyl-8-(4-chloro-2,3,5,6-tetrafluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

55 Yield: 30 mg (66%) of the title compound as an off-white solid. mp 150-151°. FDMS: m/e = 412  $\alpha[D]_{589} = +68.57$  (c =

## EP 0 703 221 A1

0.12, chloroform).

analysis:	calculated	found
C	61.25	61.04
H	4.41	4.53
N	3.40	3.22

Example 136

(4aR)(10bR)-8-benzylthio-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 150 mg of the desired white solid (52% yield). mp 137-138°. FDMS: m/e = 351.  $\alpha[D]_{589} = 59.44$  (c=0.36 in methanol).

Analysis	Calculated	Found
C	75.17	74.90
H	7.17	7.34
N	3.99	4.03

Example 137

(4aR)-(10bR)-8-phenylthiomethyl-4,10b-dimethyl-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 134 mg of the desired white solid (82% yield). mp 144-146°. FDMS: m/e = 351.  $\alpha[D]_{589} = 78.54$  (c=0.5 in methanol).

Analysis	Calculated	Found
C	75.17	74.92
H	7.17	7.27
N	3.98	4.19

Example 138

(4aR)-(10bR)-8-(2-benzothiazole)thiomethyl-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 158 mg of the desired white solid (76% yield). mp 182-184°. FDMS: m/e = 408.  $\alpha[D]_{589} = 67.31$  (c=0.5 in methanol).

Analysis	Calculated	Found
C	67.61	67.74
H	5.92	6.03
N	6.86	6.98

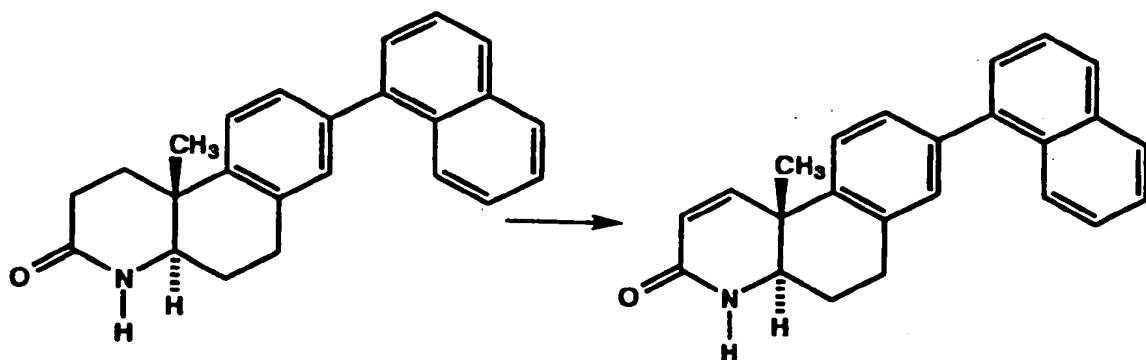
Example 139

(4aR)-(10bR)-8-diphenylmethyl-4,10b-dimethyl-1,2,3,4,-4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 33 mg of the desired product. mp 145-146°. FDMS: m/e = 396.  $\alpha[D]_{589} = 58.93$  (c=0.5 in chloroform).

The following group of examples demonstrate oxidations which provide hexahydroquinolinones in which the groups R and R<sup>1</sup> represent a bond.

Example 140

(+)-(4aR)-(10bR)-8-(1-naphthyl)-10b-methyl-3,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one



To a suspension of (+)-(4aR)-(10bR)-8-(1-naphthyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (295 mg, 0.865 mmol), in 3.5 mL of 1,4-dioxane was added DDQ (216 mg, 1.1 equiv.) followed by bistrimethylsilyl trifluoromethyl acetamide (998 mg, 4.5 equiv.), and the solution was stirred at room temperature for 2 h, then heated at 100° for 20h. The mixture was cooled to room temperature, diluted with ethyl acetate, and washed with 2 M sodium hydroxide. The organic phase was washed with brine, dried over sodium sulfate, concentrated and chromatographed on silica gel (ethyl acetate eluent) to give, after trituration from ether/hexanes, 60 mg (20%) of the title compound as a white solid. mp 199-201° (decomp.) FDMS m/e = 339.  $\alpha[D]_{589} = +35.98$  (c = 0.67, chloroform).

20

25

analysis:	calculated	found
C	84.92	84.72
H	6.24	5.98
N	4.13	3.85

30 The following examples were carried out according to the process of Example 140.

Example 141

(+)-(4aR)-(10bR)-8-(3-nitrophenyl)-10b-methyl-3,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one

35 Yield: 55 mg (21%) of the title compound as an orange solid. mp 205-206°. FDMS m/e = 334.  $\alpha[D]_{589} = +57.23$  (c = 0.66, chloroform).

40

analysis:	calculated	found
C	71.84	71.47
H	5.43	5.49
N	8.38	7.96

Example 142

(+)-(4aR)-(10bR)-8-(3-isoquinoliny)-10b-methyl-3,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one

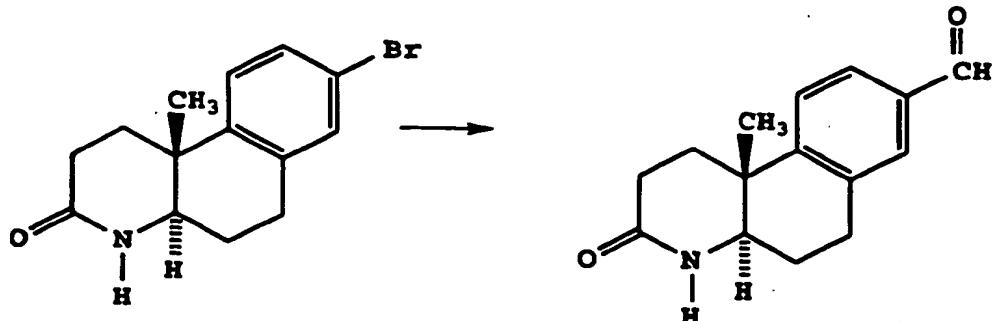
45 Yield: 18mg (24%) of the title compound as a white solid. mp 248° (decomp.) FDMS m/e = 340.

Preparation 6

50 (4aR)-(10bR)-8-formyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5

10



Methylolithium (1.5 mL, 2.1 mmol of a 1.4 M solution in diethyl ether) was added to (4aR)-(10bR)-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (0.500 g, 1.7 mmol) in 25 mL of anhydrous THF which had been cooled in a dry ice/isopropanol bath under nitrogen, and was stirred for 15 min before addition of *t*-butyllithium (2.0 mL, 3.4 mmol of a 1.7 M solution in pentane.) After 30 min, dimethylformamide (0.4 mL) was added, and the mixture was allowed to warm to 0°, and additional dimethylformamide (0.2 mL) was added. The ice bath was removed and the reaction was quenched with 1 N hydrochloric acid to make pH = 2, and then the mixture was extracted with 10% isopropanol/chloroform. The combined organic extracts were washed well with water, dried over sodium sulfate, and evaporated. The resulting product was slurried in diethyl ether before recrystallizing from 50% ethyl acetate/hexane to give off-white crystals: mp 185-189°. FD MS 243 M+; Calcd for C<sub>15</sub>H<sub>17</sub>N<sub>1</sub>O<sub>2</sub>: C, 74.05; H, 7.04; N, 5.76; Found: C, 73.85; H, 7.11; N, 5.91.

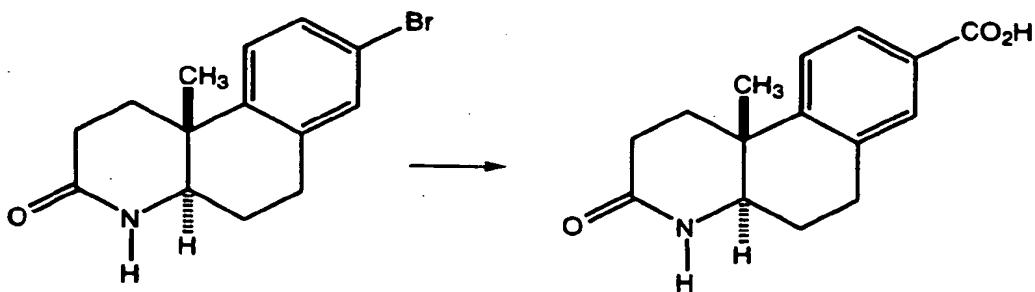
25

### Preparation 7

(4aR)-(10bR)-8-carboxy-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

30

35



In a flame-dried 3-neck round bottom flask equipped with magnetic stirrer and nitrogen inlet was dissolved (4aR)-(10bR)-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one (500 mg, 1.7 mmol). The solution was cooled to -78° and treated with ethereal methylolithium (1.7 mL, 1.4M, 2.4 mmol) added dropwise over 2 min. After further stirring for 15 min., a solution of *t*-butyllithium (2.9 mL, 1.7 M in pentane, 5.0 mmol) was added dropwise. Following complete addition, the suspension was treated with excess carbon dioxide, (generated from dry ice, dried by passage through calcium sulfate) added subsurface for 2 min. The mixture was allowed to warm to ambient temperature and was acidified with 1N aqueous hydrochloric acid. The mixture was extracted with 10% isopropanol-chloroform and the organic phase dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure afforded the crude product (520 mg) contaminated with pivalic acid. Trituration with ethyl acetate afforded product (322 mg) as a white powder (mp >320°) m/e 259.

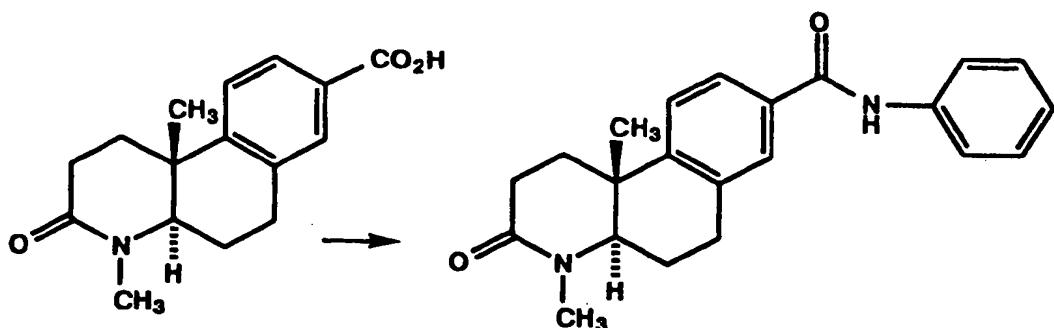
50

55

analysis:	calculated	found
C	69.48	69.51
H	6.61	6.63
N	5.40	5.18

### Example 143

(+)-(4aR)-(10bR)-4-methyl-8-(phenylcarboxamido)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



15 A 50 mL round bottom flask was charged with (+)-(4aR)-(10bR)-4-methyl-8-carboxy-10b-methyl-1,2,3,4,4a,-5,6,10b-octahydrobenzo[f]quinolin-3-one (100 mg, 0.37) and 2 mL of benzene. Oxalyl chloride (1.1 mmol) was added dropwise via syringe to the stirred mixture, followed by a catalytic amount of dimethylformamide (one drop). Allowed to stir at room temperature for 25 min, then removed volatiles in vacuo. Added 1 mL of THF, followed by a solution of aniline and pyridine (4 eq) in 1 mL of THF to the acid chloride solution at 0°. Allowed to warm to room temperature. Diluted with 50 mL of chloroform, and washed with 1 N hydrochloric acid (2 x 25 mL), 10% aq. sodium bicarbonate (2 x 25 mL), water, (2 x 25 mL), and brine (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, concentrated and chromatographed on silica (ethyl acetate eluent), to give 24 mg (19%) of the title compound as an amorphous yellow foam. FDMS: m/e = 348.

20

The following examples were carried out according to the process of Example 143.

25 Example 144

(+)-(4aR)-(10bR)-4-methyl-8-benzyloxycarbonyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 11 mg (8 %) of the title compound as an amorphous yellow foam. FDMS: m/e = 349.

30 Example 145

(+)-(4aR)-(10bR)-4-methyl-8-phenoxy carbonyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 43 mg (11%) of the title compound as a yellow solid. mp 194-196°. FDMS: m/e = 349.  $\alpha[D]_{589} = +78.53$  (c=1.00, chloroform).

35

analysis:	calculated	found
C	75.62	75.44
H	6.63	6.74
N	4.01	4.00

40

Example 146

(+)-(4aR)-(10bR)-4-methyl-8-(benzylcarboxamido)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
45 Yield: 40 mg (30%) of the title compound as an amorphous brown foam. FDMS: m/e = 362.

Example 147

(4aR)-(10bR)-4,10b-dimethyl-8-diphenylmethoxycarbonyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
50 Yield: 91 mg (57%) of the desired product. An analytical sample was recrystallized from ethyl acetate/water. mp 130-131°.  
FDMS: m/e = 439.

55

analysis:	calculated	found
C	79.24	79.49
H	6.65	6.57
N	3.19	3.28

Example 148

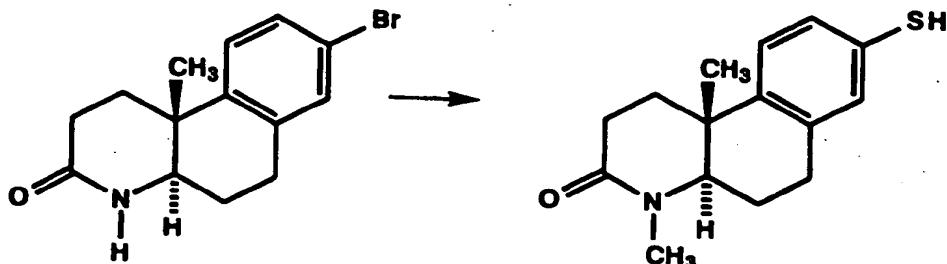
(4aR)-(10bR)-4,10b-dimethyl-8-diphenylmethylcarboxamido-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 94 mg (40%) of the desired product. mp 210-211°. FDMS: m/e = 438.

analysis:	calculated	found
C	79.42	79.27
H	6.89	6.99
N	6.39	6.42

The following preparation and example illustrates syntheses of compounds making use of an SH-substituted benzozquinolinone nucleus compound.

Preparation 8

(+)-(4aR)-(10bR)-4-methyl-8-mercaptop-10b-methyl-1,2,3,4,4a,-5,6,10b-octahydrobenzo[f]quinolin-3-one



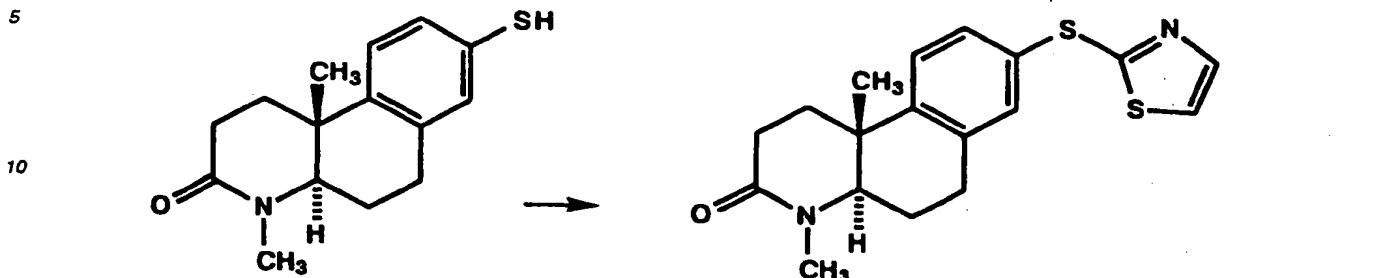
To a solution of (+)-(4aR)-(10bR)-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (5.88 g, 20 mmol) in 300 mL of anhydrous THF was added methyl lithium (158 mL, 1.4 M solution in diethyl ether) at -78°. The mixture was allowed to stir at -78° for 20 min, then t-butyllithium (26 mL, 1.7 M in pentane) was added. The mixture was stirred for an additional 90 min, and N,N-diisopropylthiuram disulfide (14.1 g, 40 mmol) in 80 mL of anhydrous THF was added at -78°. The mixture was stirred for 15 min, the cold bath was removed, and the mixture was allowed to warm to room temperature. To the mixture was added 100 mL of 1N hydrochloric acid, the organic phase was separated and washed with 1 N hydrochloric acid (200 mL), 10% sodium bicarbonate (2 X 200 mL), and brine (2 X 200 mL). The organic layer was dried over sodium sulfate, concentrated, and purified by silica gel chromatography (100% ethyl acetate - 5% methanol/ethyl acetate eluent gradient) to give 6.14 g (79%) of material which was dissolved in 61 mL of t-butanol, and potassium t-butoxide (7.42 g, 62.8 mmol) was added. The mixture was allowed to stir at room temp for 30 min (became homogeneous), cooled to 0°, and methyl iodide (62.8 mmol in 10 mL of t-butanol) was added dropwise via addition funnel. The cold bath was removed and the mixture was allowed to stir at room temperature for 16 h. The mixture was then diluted with 300 mL of ethyl acetate, the organic phase was separated, washed with brine, dried over sodium sulfate and concentrated to give 6.08 g (96%) of (+)-(4aR)-10bR)-4-methyl-8-([N,N-diisopropyl]thiuramyl)-1,2,3,4,4a,5,6,1b-octahydrobenzo[f]quinolin-3-one as a white solid. mp 181-182°. FDMS m/e = 404.  $\alpha$ [D]589 = +72.11 (c = 0.21, chloroform).

analysis:	calculated	found
C	65.30	65.11
H	7.97	7.96
N	6.92	7.07

The above thiuram (6.08 g, 15.0 mmol) was dissolved in 250 mL of trifluoroacetic acid and heated at 72° for 16 h. The solution was cooled, the volatiles were removed via rotary evaporator, the resulting oil was dissolved in chloroform, and the organic layer was washed with 10% sodium bicarbonate solution (2 X 200 mL) followed by brine (2 X 200 mL). The organic extract was dried over sodium sulfate, and concentrated to give 3.80 g (96%) of the title 8-mercaptop compound as oil, used directly without further purification. FDMS m/e = 261.

Example 149

(+)-(4aR)-(10bR)-4-methyl-8-(2-thiazoylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



A 15 mL round bottom flask was charged with (+)-(4aR)-(10bR)-4-methyl-8-mercaptop-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (100 mg, 0.38 mmol), potassium carbonate (158 mg, 1.14 mmol), 2-bromothiazole (75 mg, 0.46 mmol) and 1 mL of anhydrous dimethylformamide, fitted with a reflux condenser, and the stirred mixture was heated at 60°, under nitrogen, for 18 h. The mixture was cooled, diluted with ethyl acetate (75 mL) and washed with brine (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (ethyl acetate eluent) to give 30 mg (23%) of the title compound as an amorphous solid. mp 140-142°. FDMS: m/e = 344.

20

25

analysis:	calculated	found
C	62.76	62.52
H	5.85	5.96
N	8.13	7.93

30 The following examples were carried out according to the process of Example 149.

Example 150

(+)-(4aR)-(10bR)-4-methyl-8-(2-benzoxazoylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

35 Yield: 65 mg (45%) of the title compound as an amorphous foam. FDMS: m/e = 378.

40

analysis:	calculated	found
C	69.82	67.82
H	5.86	6.55
N	7.40	7.15

Example 151

45 (+)-(4aR)-(10bR)-4-methyl-8-(2-pyrimidinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 30 mg (23%) of the title compound as an oil. FDMS: m/e = 339

50

analysis:	calculated	found
C	67.23	67.55
H	6.24	5.88
N	12.38	12.25

Example 152

55 (+)-(4aR)-(10bR)-4-methyl-8-(2-pyrazinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 63 mg (49%) of the title compound as an off white solid. mp 94-95°. FDMS: m/e = 339.  $\alpha[D]_{589} = +88.14$  (c = 0.92, chloroform).

## EP 0 703 221 A1

analysis:	calculated	found
C	67.23	67.26
H	6.24	6.04
N	12.38	11.90

Example 153

(+)-(4aR)-(10bR)-4-methyl-8-(2-quinoxalinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 82 mg (55%) of the title compound as an amorphous foam. FDMS: m/e = 389.  $\alpha[D]_{589} = +68.96$  (c = 0.81, chloroform).

Example 154

(+)-(4aR)-(10bR)-4-methyl-8-(2-[3-phenyl]tetrazoylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 81 mg (53%) of the title compound as a white solid. mp 128-130°. FDMS: m/e = 405.  $\alpha[D]_{589} = +69.47$  (c = 0.57, chloroform).

analysis:	calculated	found
C	65.16	65.35
H	5.72	5.85
N	17.27	17.08

Example 155

(+)-(4aR)-(10bR)-4-methyl-8-(2-[5-trifluoromethyl]pyridylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 90 mg (58%) of the title compound as an amorphous solid. mp 134-140°. FDMS: m/e = 406.  $\alpha[D]_{589} = +76.80$  (c=0.42, chloroform).

analysis:	calculated	found
C	62.05	61.89
H	5.21	5.31
N	6.89	6.72

Example 156

(+)-(4aR)-(10bR)-4-methyl-8-(3-indazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 60 mg (16%) of the title compound as an oil. FDMS: m/e = 377.

Example 157

(+)-(4aR)-(10bR)-4-methyl-8-(2-[4-isopropyl]benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 57mg (34%) of the title compound as an amorphous solid. mp 166-170°. FDMS: m/e = 436.

analysis:	calculated	found
C	68.77	68.56
H	6.46	6.29
N	6.42	6.36

Example 158

(+)-(4aR)-(10bR)-4-methyl-8-(6-chloro-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

5 Yield: 86 mg (53%) of the title compound as an amorphous solid. mp 156-162°. FDMS: m/e = 429.  $\alpha[D]_{589} = +63.53$   
(c=0.66, chloroform).

analysis:	calculated	found
C	61.60	60.89
H	4.93	5.35
N	6.53	6.10

Example 159

(+)-(4aR)-(10bR)-4-methyl-8-(4-methyl-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

15 Yield: 66 mg (43%) of the title compound as an amorphous solid. mp 134-142°. FDMS: m/e = 408.  $\alpha[D]_{589} = +62.80$   
(c=0.74, chloroform).

analysis:	calculated	found
C	67.61	67.41
H	5.92	6.11
N	6.86	6.63

Example 160

(+)-(4aR)-(10bR)-4-methyl-8-(5-nitro-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

20 Yield: 97 mg (58%) of the title compound as an amorphous solid. mp 96-100°. FDMS: m/e = 439.  $\alpha[D]_{589} = +61.35$   
(c=0.64, chloroform).

analysis:	calculated	found
C	60.12	59.85
H	4.82	5.09
N	9.56	9.35

Example 161

(+)-(4aR)-(10bR)-4-methyl-8-(6-methoxy-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

40 Yield: 76 mg (47%) of the title compound as an amorphous solid. mp 102-107°. FDMS: m/e = 424.  $\alpha[D]_{589} = +64.29$   
(c=0.71, chloroform).

analysis:	calculated	found
C	65.07	64.81
H	5.70	5.98
N	6.60	6.40

Example 162

(+)-(4aR)-(10bR)-4-methyl-8-(4-fluoro-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

50 Yield: 91 mg (58%) of the title compound as an amorphous solid. mp 140-145°. FDMS: m/e = 412.  $\alpha[D]_{589} = +70.06$   
(c=0.52, chloroform).

analysis:	calculated	found
C	64.05	64.29
H	5.13	5.21
N	6.79	6.97

Example 163

10 (+)-(4aR)-(10bR)-4-methyl-8-(2-naphtho<1,2-d>-thiazolythio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

Yield: 94 mg (56%) of the title compound as an amorphous solid. mp 179-184°. FDMS: m/e = 444.  $\alpha[D]_{589} = +60.59$  (c=0.67, chloroform).

analysis:	calculated	found
C	70.24	69.95
H	5.44	5.50
N	6.30	6.16

Example 164

(+)-(4aR)-(10bR)-4-methyl-8-(4-chloro-2-benzothiazolythio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 80mg (49%) of the title compound as an amorphous solid. mp 207-209°. FDMS: m/e = 429  $\alpha[D]_{589} = +63.86$  (c=0.57, chloroform).

analysis:	calculated	found
C	61.60	61.80
H	4.93	5.13
N	6.53	6.45

Example 165

35 (+)-(4aR)-(10bR)-4-methyl-8-(5,6-dichloro-2-benzothiazolythio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]-quinolin-3-one

Yield: 54 mg (31%) of the title compound as an amorphous foam. FDMS: m/e = 463.

Example 166

(+)-(4aR)-(10bR)-4-methyl-8-(5-nitro-2-pyridinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 106 mg (73%) of the title compound as an amorphous foam. mp 188-191°. FDMS: m/e = 383.  $\alpha[D]_{589} = +57.07$  (c=0.68, chloroform).

analysis:	calculated	found
C	62.64	62.09
H	5.52	5.76
N	10.96	10.40

Example 167

(+)-(4aR)-(10bR)-4-methyl-8-(3-nitro-2-pyridinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

55 Yield: 95 mg (65%) of the title compound as an amorphous foam. mp 80-84°. FDMS: m/e = 383.  $\alpha[D]_{589} = +73.78$  (c=0.49, chloroform).

5

analysis:	calculated	found
C	62.64	62.94
H	5.52	5.68
N	10.96	10.92

Example 168

10 (+)-(4aR)-(10bR)-4-methyl-8-(6-nitro-2-quinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 88 mg (53%) of the title compound as a tan solid. mp 195-196°. FDMS: m/e = 433.  $\alpha[D]_{589} = +64.56$  (c=0.78, chloroform).

15

analysis:	calculated	found
C	66.49	66.25
H	5.35	5.51
N	9.69	9.41

Example 169

20 (+)-(4aR)-(10bR)-4-methyl-8-(5-nitro-2-quinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 29 mg (56%) of the title compound as an amorphous foam. mp 149-154°. FDMS: m/e = 433.  $\alpha[D]_{589} = +60.00$  (c=0.10, chloroform).

25

Example 170

25 (+)-(4aR)-(10bR)-4-methyl-8-(8-nitro-2-quinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 90 mg (55%) of the title compound as a solid. mp 199-200°. FDMS: m/e = 433.  $\alpha[D]_{589} = +76.80$  (c=0.42, chloroform).

30

35

analysis:	calculated	found
C	66.49	66.28
H	5.35	5.52
N	9.69	9.47

Example 171

40 (+)-(4aR)-(10bR)-4-methyl-8-(6-phenyl-3-pyridazinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 77 mg (49%) of the title compound as an amorphous solid. mp 199-200°. FDMS: m/e = 415.  $\alpha[D]_{589} = +67.26$  (c=0.63, chloroform).

45

analysis:	calculated	found
C	72.26	72.06
H	6.06	6.21
N	10.11	9.93

50

Example 172

45 (+)-(4aR)-(10bR)-4-methyl-8-(2-phenyl-4-quinazolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 112 mg (63%) of the title compound as an off white solid. mp 185-193°. FDMS: m/e = 465.  $\alpha[D]_{589} = +49.59$  (c = 0.57, chloroform).

analysis:	calculated	found
C	74.81	73.56
H	5.84	5.94
N	9.02	8.95

5

Example 173

10 (+)-(4aR)-(10bR)-4-methyl-8-(6-fluoro-2-quinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 96 mg (62%) of the title compound as a solid. mp 152-155°. FDMS: m/e = 406.  $\alpha[D]_{589} = +63.16$  (c=0.61, chloroform).

15

analysis:	calculated	found
C	70.91	70.76
H	5.70	5.83
N	6.89	6.81

20

Example 174

(+)-(4aR)-(10bR)-4-methyl-8-(8-fluoro-2-quinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

25 Yield: 78 mg (50%) of the title compound as an amorphous foam. FDMS: m/e = 406.  $\alpha[D]_{589} = +63.29$  (c = 0.56, chloroform).

30

analysis:	calculated	found
C	70.91	71.15
H	5.70	5.82
N	6.89	6.94

35

Example 175

(+)-(4aR)-(10bR)-4-methyl-8-(4-thieno[3,2-c]pyridylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 37 mg (25%) of the title compound as a white solid. mp 196-197°. FDMS: m/e = 394.  $\alpha[D]_{589} = +75.17$  (c = 0.57, chloroform).

40

analysis:	calculated	found
C	66.97	66.70
H	5.62	5.70
N	7.10	6.88

45

Example 176

(+)-(4aR)-(10bR)-4-methyl-8-(10-oxo-10H-2-pyridazino[6,1-b]quinazolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

50 Yield: 103 mg (62%) of the title compound as an amorphous foam. mp 110-114°. FDMS: m/e = 456.  $\alpha[D]_{589} = +54.77$  (c = 0.49, chloroform).

55

analysis:	calculated	found
C	68.40	68.22
H	5.30	5.31
N	12.27	12.01

Example 177

(+)-(4aR)-(10bR)-4-methyl-8-(3-phenyl-1-isoquinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 64 mg (42%) of the title compound as an off white solid. mp 183-189°. FDMS: m/e = 464.  $\alpha[D]_{589} = +54.61$  (c = 0.53, chloroform).

	analysis:	calculated	found
10	C	77.55	77.26
	H	6.07	6.16
	N	6.03	6.16

Example 178

(+)-(4aR)-(10bR)-4-methyl-8-(3-methyl-2-quinolinylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 9 mg (16%) of the title compound as an amorphous foam. mp 185-193°. FDMS: m/e = 402.

Example 179

(+)-(4aR)-(10bR)-4-methyl-8-[3-phenyl-4-(4-methoxyphenyl)-2-quinolinylthio]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20 Yield: 56 mg (43%) of the title compound as an off white solid. mp 239-242°. FDMS: m/e = 570.  $\alpha[D]_{589} = +45.00$  (c = 1.40, chloroform).

	analysis:	calculated	found
30	C	77.86	77.58
	H	6.00	6.12
	N	4.91	4.94

Example 180

35 (+)-(4aR)-(10bR)-4-methyl-8-(3-[1,2-benzisothiazolyl]thio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 54 mg (36%) of the title compound as an amorphous foam. FDMS: m/e = 394.

	analysis:	calculated	found
40	C	66.97	67.05
	H	5.62	5.83
	N	7.10	7.03

Example 181

(+)-(4aR)-(10bR)-4-methyl-8-(2-[4,6-diphenyl]pyridylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

45 Yield: 40 mg (27%) of the title compound as an amorphous solid. FDMS: m/e = 490.  $\alpha[D]_{589} = +37.97$  (c = 0.39, chloroform).

Example 182

(+)-(4aR)-(10bR)-4-methyl-8-(4-methoxy-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

55 Yield: 107 mg (66%) of the title compound as an off white solid. mp 200-205°. FDMS: m/e = 424.  $\alpha[D]_{589} = +60.56$  (c = 0.96, chloroform).

## EP 0 703 221 A1

analysis:	calculated	found
C	65.07	64.43
H	5.70	5.55
N	6.60	7.81

5

Example 183

10 (4aR)-(10bR)-4-methyl-8-(4-bromo-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one  
Yield: 142 mg (79%) of the title compound as an off white solid. mp 206-210°. FDMS: m/e = 474.  $\alpha[D]_{589} = +56.2S$  (c = 0.59, chloroform).

15

analysis:	calculated	found
C	55.81	55.63
H	4.47	4.62
N	5.92	6.16

20

Example 184

(4aR)-(10bR)-4-methyl-8-(4-phenyl-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one  
25 Yield: 110 mg (61%) of the title compound as an amorphous foam. FDMS: m/e = 470.  $\alpha[D]_{589} = +53.51$  (c = 0.66, chloroform).

30

analysis:	calculated	found
C	71.46	71.22
H	5.57	5.69
N	5.95	5.82

35

Example 185

(4aR)-(10bR)-4-methyl-8-(4,7-dimethyl-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]qui-  
nolin-3-one  
Yield: 111 mg (69%) of the title compound as an amorphous foam. FDMS: m/e = 422.  $\alpha[D]_{589} = +63.27$  (c=0.95, chlo-  
roform).

40

Example 186

(4aR)-(10bR)-4-methyl-8-(4-propyl-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one  
45 Yield: 116 mg (70%) of the title compound as an amorphous solid. mp 109-111°. FDMS: m/e = 436.  $\alpha[D]_{589} = +45.00$  (c=0.80, chloroform).

50

analysis:	calculated	found
C	68.77	68.50
H	6.46	6.57
N	6.42	6.44

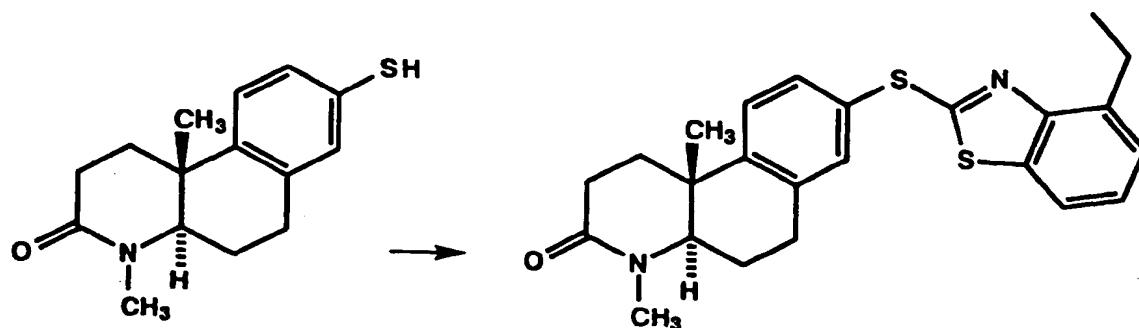
55

Example 187

(4aR)-(10bR)-4-methyl-8-(4-ethyl-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

5

10



15 A 200 mL round bottom flask was charged with (+)-(4aR)-(10bR)-4-methyl-8-mercaptop-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (1.36g, 5.20 mmol), potassium carbonate (2.16 g, 15.6 mmol), 2-chloro-4-ethylbenzothiazole (1.23g, 6.20 mmol) and 14 mL of anhydrous dimethylformamide, fitted with a reflux condenser, and the stirred mixture was heated at 60°, under nitrogen, for 18h. The mixture was cooled, diluted with ethyl acetate (750 mL) and washed with brine (6 x 250 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (80% ethyl acetate/hexanes eluent) to give 1.51g (69%) of the title compound as an amorphous foam. FDMS: m/e = 422.  $\alpha[D]_{589} = +62.74$  (c=0.67, chloroform).

25

analysis:	calculated	found
C	68.21	68.40
H	6.20	6.22
N	6.63	6.49

#### Example 188

30

(+)-(4aR)-(10bR)-4-methyl-8-(4-trifluoromethoxy-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 141 mg (77%) of the title compound as a white solid. mp 168-173°. FDMS: m/e = 478.  $\alpha[D]_{589} = +57.89$  (c = 0.59, chloroform).

35

analysis:	calculated	found
C	57.73	57.50
H	4.42	4.52
N	5.85	5.78

#### Example 189

45

(+)-(4aR)-(10bR)-4-methyl-8-[4,7-di(t-butyl)-2-benzothiazolylthio]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 33 mg (17 %) of the title compound as an amorphous foam. FDMS: m/e = 506.

#### Example 190

50

(+)-(4aR)-(10bR)-4-methyl-8-(4-methyl-7-trifluoromethyl-2-benzothiazolylthio)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 94 mg (52%) of the title compound as an amorphous foam. mp 50-54°. FDMS: m/e = 476.

55

analysis:	calculated	found
C	60.49	60.79
H	4.86	5.14
N	5.88	5.75

## EP 0 703 221 A1

Example 191

(+)-(4aR)-(10bR)-8-(3-isoquinolinylmethylthio)-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one  
 Yield: crystalline solid (91 mg), mp = 129-130°. m/e 402. OR (c=1.0, methanol) @ 589 nM, +64.2°, @ 365 nM, +226.7°.

5

analysis:	calculated	found
C	74.59	74.87
H	6.51	6.45
N	6.96	7.09

10

Example 192

(+)-(4aR)-(10bR)-8-(2-benzothiazolylmethylthio)-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one  
 Yield: a crystalline solid (55 mg), mp = 78-80°. m/e 408. OR (c=0.3, methanol) @ 589 nM, +66.3°.

15

analysis:	calculated	found
C	67.61	67.51
H	5.92	6.05
N	6.86	6.63

20

Example 193

(4aR)-(10bR)-4,10b-dimethyl-8-(7-chloro-2-benzothiazolylthio)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one  
 Yield: 195 mg of the desired product. mp 90-91°. FDMS: m/e = +428.

25

analysis:	calculated	found
C	61.60	61.83
H	4.93	5.09
N	6.53	6.49

30

Example 194

(4aR)-(10bR)-4,10b-dimethyl-8-(5-chloro-2-benzothiazolylthio)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one  
 Yield: 56 mg of the desired product. mp 179-180°. FDMS: m/e = +428.

35

analysis:	calculated	found
C	61.60	61.30
H	4.93	4.89
N	6.53	6.51

40

Example 195

(4aR)-(10bR)-8-diphenylmethylthio-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one  
 Yield: 146 mg of the desired product. mp 102-104°. FDMS: m/e = +427.  $\alpha[D]_{589} = 60.28$ .

50

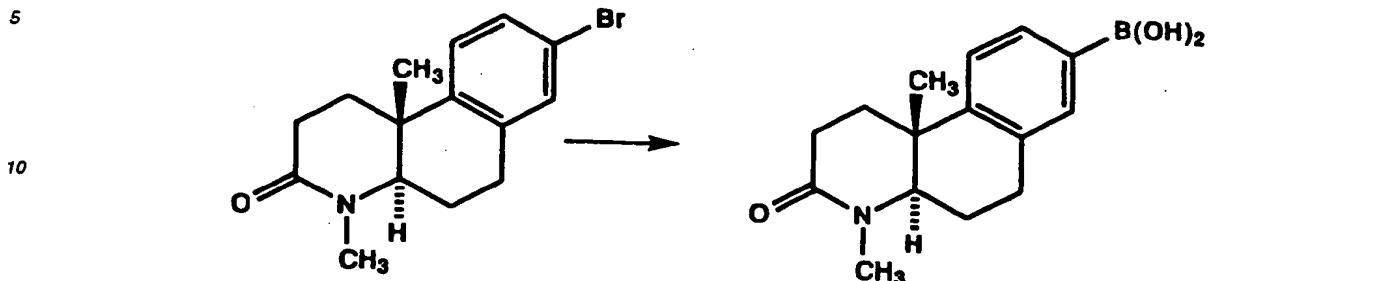
analysis:	calculated	found
C	78.65	78.65
H	6.84	6.72
N	3.28	3.47

55

The following preparation and examples illustrate the synthesis of compounds of the present invention through an intermediate having a boronic acid substituent on the benzoquinolinone nucleus.

Preparation 9

(+)-(4aR)-(10bR)-4-methyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one-8-boronic acid

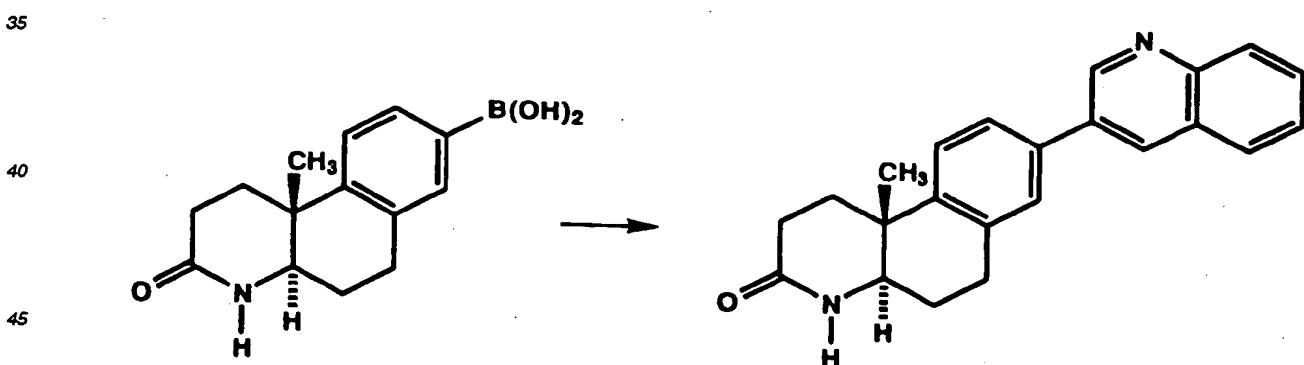


To a solution of (+)-(4aR)-(10bR)-4-methyl-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (5.0 g, 16.2 mmol) in 500 mL of anhydrous THF was added t-butyllithium (37.5 mL, 1.3 M solution in cyclohexane) at -78°. The mixture was allowed to stir at -78° for 75 min, and a solution of triisopropyl borate (2.0 equiv.) in 12.5 mL of anhydrous THF was added dropwise. The mixture was stirred for an additional 45 min, then the cold bath was removed, and the mixture was allowed to warm to room temperature. The mixture was quenched with 5 N hydrochloric acid (50 mL), and volatiles were removed on rotary evaporator. The mixture was then treated with 35 mL of 5 N sodium hydroxide, and was extracted with THF (300 mL). The organic extract was dried over sodium sulfate, filtered, and concentrated. The resulting solid was heated in boiling ethyl acetate for 15 min, followed by filtration (while still hot), to yield 3.65 g (82%) of the title compound as a white solid. mp 200° (decomp.)  $\alpha[D]_{589} = +72.27$  (c = 0.89, methanol).

analysis:	calculated	found
C	65.96	65.74
H	7.38	7.73
N	5.13	4.94

Example 196

(+)-(4aR)-(10bR)-8-(3-quinolinyl)-10b-methyl-1,2,3,4,4a,-5,6,10b-octahydrobenzo[f]quinolin-3-one



A 15 mL round bottom flask was charged with (+)-(4aR)-(10bR)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one-8-boronic acid (168 mg, 0.65 mmol), tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.02 mmol), 3-bromoquinoline (135 mg, 0.65 mmol), 0.65 mL of aqueous 2 M sodium carbonate and 2mL of THF, fitted with a reflux condenser, and the stirred mixture was heated at 80°, under nitrogen, for 24 h. The mixture was cooled, diluted with chloroform (75 mL) and washed with brine (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (5% methanol / ethyl acetate eluent) to give 141 mg (63%) of the title compound as a white solid. mp 265-266°. FDMS: m/e = 342.  $\alpha[D]_{589} = +88.70$  (c = 0.84, chloroform).

55 The following examples were carried out according to the process of Example 196.

Example 197

(+)-(4aR)-(10bR)-8-(4-[2,8-bistrifluoromethyl]quinolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 186 mg (60%) of the title compound as a white solid. mp 214-215°. FDMS: m/e = 478.  $\alpha[D]_{589} = +62.00$  (c = 1.10, chloroform)

Example 198

10 (+)-(4aR)-(10bR)-8-(2-thiazolyl)-10b-methyl-1,2,3,4,4a,-5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 64 mg (35%) of the title compound as a white solid. mp 206-207°. FDMS: m/e = 298.  $\alpha[D]_{589} = +101.7$  (c = 0.97, chloroform).

Example 199

15 (+)-(4aR)-(10bR)-8-(5-nitro-2-pyridinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 71 mg of the title compound as a white solid. mp 123-124°. FDMS: m/e = 337.  $\alpha[D]_{589} = +85.60$  (c = 0.61, chloroform).

Example 200

(+)-(4aR)-(10bR)-4-methyl-8-(4-isoquinolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 110 mg (47%) of the title compound as an amorphous foam. FDMS: m/e = 356.  $\alpha[D]_{589} = +67.82$  (c=0.40, methanol).

25

30

analysis:	calculated	found
C	80.87	80.57
H	6.79	6.82
N	7.86	7.69

Example 201

(+)-(4aR)-(10bR)-4-methyl-8-(3-quinolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

35 Yield: 130 mg (56%) of the title compound as an amorphous solid. mp: 180-185°. FDMS: m/e = 356.  $\alpha[D]_{589} = +80.22$  (c=0.37, chloroform).

40

45

analysis:	calculated	found
C	80.87	80.65
H	6.79	6.52
N	7.86	7.68

Example 202

(+)-(4aR)-(10bR)-4-methyl-8-(5-nitro-2-pyridinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 148 mg (65%) of the title compound as an amorphous foam. mp 70-80°. FDMS: m/e = 351.  $\alpha[D]_{589} = +85.59$  (c = 0.48, chloroform)

50

55

analysis:	calculated	found
C	68.26	67.81
H	6.02	6.18
N	11.96	11.42

Example 203

(+)-(4aR)-(10bR)-4-methyl-8-[2,8-bis(trifluoromethyl)-4-quinolinyl]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]

## 5 quinolin-3-one

Yield: 153 mg (48%) of the title compound as an amorphous foam. mp 100-106°. FDMS: m/e = 492.  $\alpha[D]_{589} = +51.86$  (c = 0.47, chloroform).

analysis:	calculated	found
C	63.41	63.25
H	4.50	4.77
N	5.69	5.40

10

Example 204

(+)-(4aR)-(10bR)-4-methyl-8-(4-methylsulfonylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 137 mg (55%) of the title compound as a white solid. mp 229°. FDMS: m/e = 383.  $\alpha[D]_{589} = +28.24$  (c = 0.23, chloroform).

analysis:	calculated	found
C	68.90	69.10
H	6.57	6.65
N	3.65	3.89

20

Example 205

25

(+)-(4aR)-(10bR)-4-methyl-8-(2,3,4,5,6-pentafluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 97 mg (38%) of the title compound as an amorphous foam. mp 92-100°. FDMS: m/e = 395.  $\alpha[D]_{589} = +64.15$  (c = 0.42, chloroform).

30

Example 206

(+)-(4aR)-(10bR)-4-methyl-8-(3,4,5-trifluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

35 Yield: 117 mg (50%) of the title compound as an amorphous wax. FDMS: m/e = 359.  $\alpha[D]_{589} = +75.86$  (c = 0.47, chloroform).

analysis:	calculated	found
C	70.18	70.41
H	5.61	5.81
N	3.90	3.78

40

Example 207

45

(+)-(4aR)-(10bR)-4-methyl-8-(1-oxo-5-indanyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 91 mg (39%) of the title compound as a white solid. mp 175-178°. FDMS: m/e = 359.  $\alpha[D]_{589} = +74.81$  (c = 0.53, chloroform).

50

analysis:	calculated	found
C	80.19	79.08
H	7.01	7.01
N	3.90	4.08

55

Example 208

(+)-(4aR)-(10bR)-4-methyl-8-(2-fluoro-3-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

EP 0 703 221 A1

Yield: 130 mg (51%) of the title compound as an oil. FDMS: m/e = 391.  $\alpha[D]_{589} = +68.49$  (c = 0.38, chloroform).

Example 209

5    (+)-(4aR)-(10bR)-4-methyl-8-(3-{1-benzyl-4-piperidinylcarboxamido}phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 148 mg (44%) of the title compound as an amorphous foam. FDMS: m/e = 521.  $\alpha[D]_{589} = +53.50$  (c = 0.45, chloroform).

10

analysis:	calculated	found
C	78.28	77.50
H	7.53	7.60
N	8.05	7.65

15    Example 210

(+)-(4aR)-(10bR)-4-methyl-8-(2-fluoro-4-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 20    Yield: 171 mg (67%) of the title compound as an amorphous solid. mp 72-79°. FDMS: m/e = 391.  $\alpha[D]_{589} = +62.50$  (c=0.48, chloroform).

25

analysis:	calculated	found
C	67.51	67.72
H	5.41	5.65
N	3.58	3.33

30    Example 211

(+)-(4aR)-(10bR)-4-methyl-8-(2-fluoro-5-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 113 mg (44%) of the title compound as an oil. FDMS: m/e = 391.  $\alpha[D]_{589} = +55.84$  (c = 0.34, chloroform).

35

analysis:	calculated	found
C	67.51	67.73
H	5.41	5.62
N	3.58	3.31

40    Example 212

(+)-(4aR)-(10bR)-4-methyl-8-(3-methylthiophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 110 mg (48%) of the title compound as an oily solid. FDMS: m/e = 351.  $\alpha[D]_{589} = +90.00$  (c=0.17, chloroform).

45

analysis:	calculated	found
C	75.17	75.02
H	7.17	7.13
N	3.98	3.77

50    Example 213

(+)-(4aR)-(10bR)-4-methyl-8-(4-carboxamidophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 21 mg (9%) of the title compound as amorphous foam. mp 177-189° (decomp.) FDMS: m/e = 348.

Example 214

(+)-(4aR)-(10bR)-4-methyl-8-[2-oxo-3-(N,N-diethylcarboxamido)-1-2H-benzopyran-6-yl]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 138 mg (45%) of the title compound as an amorphous foam. mp 120-125°. FDMS: m/e = 472.  $\alpha[D]_{589} = +54.69$  (c = 0.49, chloroform).

analysis:	calculated	found
C	73.71	73.49
H	6.82	6.85
N	5.93	5.86

Example 215

(+)-(4aR)-(10bR)-4-methyl-8-[2-(t-butylcarbonylamino)-5-pyridinyl]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 84 mg (32%) of the title compound as a brown solid. mp 248-250°. FDMS: m/e = 405.  $\alpha[D]_{589} = +70.74$  (c = 0.45, chloroform).

analysis:	calculated	found
C	74.04	74.31
H	7.70	7.70
N	10.36	9.85

Example 216

(+)-(4aR)-(10bR)-4-methyl-8-(3-fluoro-5-trifluoromethylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

30 Yield: 145 mg (57%) of the title compound as an oil. FDMS: m/e = 391.  $\alpha[D]_{589} = +67.32$  (c = 0.55, chloroform).

analysis:	calculated	found
C	67.51	67.90
H	5.41	5.73
N	3.58	3.27

Example 217

(+)-(4aR)-(10bR)-4-methyl-8-(5-nitro-2-thienyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

40 Yield: 118 mg (51%) of the title compound as a white solid. mp 147-149°. FDMS: m/e = 356.  $\alpha[D]_{589} = +83.48$  (c = 0.54, chloroform).

analysis:	calculated	found
C	64.02	64.30
H	5.66	5.78
N	7.86	7.57

Example 218

(+)-(4aR)-(10bR)-4-methyl-8-(5-chloro-2-thienyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

50 Yield: 125 mg (56%) of the title compound as an oil. FDMS: m/e = 345.  $\alpha[D]_{589} = +74.03$  (c = 0.51, chloroform).

## EP 0 703 221 A1

5

analysis:	calculated	found
C	66.98	67.39
H	5.83	5.90
N	4.05	3.86

Example 219

10 (4aR)-(10bR)-4-methyl-8-(4-chloro-3-fluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 125 mg (56%) of the title compound as an amorphous foam. FDMS: m/e = 357.  $\alpha[D]_{589} = +74.28$  (c = 0.35, chloroform).

15

analysis:	calculated	found
C	70.48	70.54
H	5.91	6.04
N	3.91	3.81

20

Example 220

(4aR)-(10bR)-4-methyl-8-(4-sulfonamidophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 34 mg (14%) of the title compound as a white solid. mp 200° (decomp.) FDMS: m/e = 384.  $\alpha[D]_{589} = +201.8$  (c = 0.43, chloroform).

25

analysis:	calculated	found
C	65.60	65.83
H	6.29	6.46
N	7.29	7.52

Example 221

35 (4aR)-(10bR)-4-methyl-8-[4-(4-chlorobutyl)phenyl]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 113 mg (42%) of the title compound an oil. FDMS: m/e = 409.  $\alpha[D]_{589} = +60.00$  (c = 0.18, chloroform).

40

analysis:	calculated	found
C	73.25	72.91
H	6.88	6.80
N	3.42	3.33

Example 222

45 (4aR)-(10bR)-4-methyl-8-(4-[(2-t-butylcarbonylamino)-5-thienyl]phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 88 mg (28%) of the title compound a brown solid. mp 240° (decomp.) FDMS: m/e = 487.  $\alpha[D]_{589} = +61.73$  (c = 0.47, chloroform).

50

analysis:	calculated	found
C	71.43	71.62
H	6.82	7.00
N	8.62	8.05

55

Example 223

(+)-(4aR)-(10bR)-4-methyl-8-(2,3-dioxo-5-indoliny)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 36 mg (15%) of the title compound as a white solid. mp >250° FDMS: m/e = 374.  $\alpha[D]_{589} = +75.33$  (c = 0.53, chloroform).

analysis:	calculated	found
C	73.78	73.29
H	5.92	5.98
N	7.48	7.22

Example 224

(+)-(4aR)-(10bR)-4-methyl-8-(2-(2-dimethylaminoethyl)-1H-benzo<de>isoquinolin-6-yl-1,3-(2H)dione)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 141 mg (44%) of the title compound as a white solid. mp 190-192°. FDMS: m/e = 495.  $\alpha[D]_{589} = +74.71$  (c=0.53, chloroform).

analysis:	calculated	found
C	75.13	74.94
H	6.71	6.33
N	8.48	8.22

Example 225

(+)-(4aR)-(10bR)-4-methyl-8-(2aR,4S-1-benzoyl-4-dipropylamino-2,2a,3,4-tetrahydrobenz[cd]-1H-indol-7-yl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 64 mg (17%) of the title compound as an amorphous foam. mp 110-115°. FDMS: m/e = 589.  $\alpha[D]_{589} = +80.14$  (c = 0.46, chloroform).

analysis:	calculated	found
C	79.42	79.58
H	8.03	8.06
N	7.12	6.73

Example 226

(+)-(4aR)-(10bR)-4-methyl-8-(2aR,4S-1-benzoyl-4-amino-2,2a,3,4-tetrahydrobenz[cd]-1H-indol-7-yl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 187 mg (57%) of the title compound as an amorphous foam. mp 134-136°. FDMS: m/e = 505.

Example 227

(+)-(4aR)-(10bR)-4-methyl-8-(3,5-difluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 137 mg (62%) of the title compound as an oil. FDMS: m/e = 341.  $\alpha[D]_{589} = +79.29$  (c = 0.28, chloroform).

analysis:	calculated	found
C	73.88	73.40
H	6.20	6.11
N	4.10	3.99

Example 228

(+)-(4aR)-(10bR)-4-methyl-8-(2,6-difluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

EP 0 703 221 A1

Yield: 98 mg (44%) of the title compound as an amorphous solid. mp 125-130° FDMS: m/e = 341.  $\alpha[D]_{589} = +71.79$  (c = 0.58, chloroform).

analysis:	calculated	found
C	73.88	74.13
H	6.20	6.32
N	4.10	3.87

10 Example 229

(+)-(4aR)-(10bR)-4-methyl-8-(2,5-difluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 105 mg (47%) of the title compound as an oil. FDMS: m/e = 341.  $\alpha[D]_{589} = +70.96$  (c = 0.38, chloroform).

analysis:	calculated	found
C	73.88	74.01
H	6.20	6.43
N	4.10	3.76

20 Example 230

(+)-(4aR)-(10bR)-4-methyl-8-(2,4,6-trifluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 116 mg (50%) of the title compound as an oil. FDMS: m/e = 359.  $\alpha[D]_{589} = +68.65$  (c = 0.35, chloroform).

analysis:	calculated	found
C	70.18	70.15
H	5.61	5.86
N	3.90	3.69

30 Example 231

(+)-(4aR)-(10bR)-4-methyl-8-(2,4-difluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 106 mg (48%) of the title compound as white solid. mp 108-112°. FDMS: m/e = 341.  $\alpha[D]_{589} = +82.90$  (c = 0.52, chloroform).

analysis:	calculated	found
C	73.88	73.94
H	6.20	6.33
N	4.10	4.05

40 Example 232

(+)-(4aR)-(10bR)-4-methyl-8-(2,3,4-trifluorophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 100 mg (43%) of the title compound as a white solid. mp 100-102°. FDMS: m/e = 359  $\alpha[D]_{589} = +7837$  (c = 0.33, chloroform).

analysis:	calculated	found
C	70.18	70.47
H	5.61	5.80
N	3.90	3.78

50 Example 233

(+)-(4aR)-(10bR)-4-methyl-8-(4-[4-nitrobenzyl]thiophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinol-

## lin-3-one

Yield: 166 mg (54%) of the title compound as an oily solid. FDMS: m/e = 472.  $\alpha[D]_{589} = +65.63$  (c=0.41, chloroform).

analysis:	calculated	found
C	71.16	71.63
H	5.97	6.21
N	5.93	6.26

## Example 234

(+)-(4aR)-(10bR)-4-methyl-8-(2-(2-[1-morpholino]ethyl)-1H-benzo<de>isoquinolin-6-yl-1,3-(2H)dione)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 176 mg (50%) of the title compound as an amorphous solid. mp 100-105°. FDMS: m/e = 537.  $\alpha[D]_{589} = +45.10$  (c=0.53, chloroform).

analysis:	calculated	found
C	73.72	73.46
H	6.56	6.73
N	7.82	7.55

## Example 235

(+)-(4aR)-(10bR)-4-methyl-8-(4-pyridinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 85 mg (43%) of the title compound as an oil. FDMS: m/e = 306.

analysis:	calculated	found
C	78.40	78.56
H	7.24	7.00
N	9.14	8.68

## Example 236

(+)-(4aR)-(10bR)-4-methyl-8-(1-p-toluenesulfonylindol-5-yl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 49 mg (15%) of the title compound as an amorphous foam. FDMS: m/e = 498.

analysis:	calculated	found
C	72.26	71.04
H	6.06	6.32
N	5.62	4.94

## Example 237

(+)-(4aR)-(10bR)-4-methyl-8-(1-acetyl-7-nitroindolin-5-yl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 63 mg (22%) of the title compound a yellow solid. mp 235-240°. FDMS: m/e = 433.  $\alpha[D]_{589} = +65.72$  (c = 0.99, chloroform).

analysis:	calculated	found
C	69.27	69.39
H	6.28	6.55
N	9.69	9.54

## EP 0 703 221 A1

Example 238

(+)-(4aR)-(10bR)-4-methyl-8-(1-acetylindolin-5-yl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 67 mg (26%) of the title compound as a yellow solid. mp 197-200°. FDMS: m/e = 388.  $\alpha[D]_{589} = +77.92$  (c = 0.36, chloroform).

analysis:	calculated	found
C	77.29	77.04
H	7.26	7.00
N	7.21	7.12

Example 239

(+)-(4aR)-(10bR)-4-methyl-8-(8-quinolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 88 mg (38%) of the title compound as a tan solid. mp 205-207°. FDMS: m/e = 356.  $\alpha[D]_{589} = +76.28$  (c = 0.47, chloroform).

analysis:	calculated	found
C	80.87	80.66
H	6.79	6.69
N	7.86	7.76

Example 240

(+)-(4aR)-(10bR)-4-methyl-8-(5-quinolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 128 mg (55%) of the title compound as an amorphous foam. mp 100-104°. FDMS: m/e = 356.  $\alpha[D]_{589} = +61.77$  (c = 0.35, chloroform).

analysis:	calculated	found
C	80.87	79.55
H	6.79	6.92
N	7.86	7.60

Example 241

(+)-(4aR)-(10bR)-4-methyl-8-(5-isoquinolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 98 mg (42%) of the title compound as an amorphous solid. mp 182-184°. FDMS: m/e = 356.  $\alpha[D]_{589} = +57.25$  (c = 0.49, chloroform).

analysis:	calculated	found
C	80.87	80.28
H	6.79	6.86
N	7.86	7.43

Example 242

(+)-(4aR)-(10bR)-4-methyl-8-(2-pyridinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 98 mg (49%) of the title compound as an oil. FDMS: m/e = 306.  $\alpha[D]_{589} = +83.48$  (c = 0.38, chloroform).

analysis:	calculated	found
C	78.40	77.73
H	7.24	6.96
N	9.14	9.07

Example 243

(+)-(4aR)-(10bR)-4-methyl-8-(2,5-difluoro-4-nitrophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 128 mg (51%) of the title compound as an amorphous solid. mp: 130-140°. FDMS: m/e = 386.  $\alpha[D]_{589} = +73.44$  (c=0.53, chloroform).

	analysis:	calculated	found
10	C	65.28	66.70
	H	5.22	5.69
	N	7.25	7.64

Example 244

15 (+)-(4aR)-(10bR)-4-methyl-8-(6-quinolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 107 mg (46%) of the title compound as an amorphous solid. mp 185-190°. FDMS: m/e = 356.  $\alpha[D]_{589} = +78.73$  (c = 0.56, chloroform).

	analysis:	calculated	found
20	C	80.87	80.13
	H	6.79	6.74
	N	7.86	6.99

Example 245

25 (+)-(4aR)-(10bR)-4-methyl-8-(1-hydroxy-5-indanyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 79 mg (34%) of the title compound as an amorphous solid. mp: 185-190°. FDMS: m/e = 361.  $\alpha[D]_{589} = +77.38$  (c=0.35, chloroform).

	analysis:	calculated	found
30	C	79.74	79.01
	H	7.53	7.53
	N	3.87	3.79

Example 246

40 (+)-(4aR)-(10bR)-4-methyl-8-[2-(4-[N-benzyl]piperidinyl)-1H-benzo<de>isoquinolin-6-yl]-1,3-(2H)dione]-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 197 mg (51%) of the title compound as an amorphous foam. FDMS: m/e = 597.  $\alpha[D]_{589} = +51.09$  (c=0.58, chloroform).

	analysis:	calculated	found
45	C	78.36	76.08
	H	6.58	6.80
	N	7.03	6.40

Example 247

50 (+)-(4aR)-(10bR)-4-methyl-8-(2-quinolinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 126 mg (54%) of the title compound as an amorphous foam. mp 140-145°. FDMS: m/e = 356.  $\alpha[D]_{589} = +74.01$  (c = 0.46, chloroform).

analysis:	calculated	found
C	80.87	80.56
H	6.79	6.88
N	7.86	7.45

5

Example 248

10 (+)-(4aR)-(10bR)-4-methyl-8-(2-oxo-1-benzopyran-6-yl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 108 mg (40%) of the title compound an amorphous solid. mp 180° (decomp.) FDMS: m/e = 373.  $\alpha[D]_{589} = +40.48$  (c = 0.42, chloroform).

15

analysis:	calculated	found
C	77.19	76.90
H	6.21	6.48
N	3.75	4.02

20

Example 249

(+)-(4aR)-(10bR)-4-methyl-8-(6-benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 106 mg (47%) of the title compound as an amorphous solid. mp 183-187°. FDMS: m/e = 362.  $\alpha[D]_{589} = +87.80$  (c = 0.55, chloroform).

30

analysis:	calculated	found
C	72.90	72.63
H	6.12	6.30
N	7.73	7.49

Example 250

35 (+)-(4aR)-(10bR)-4-methyl-8-(1-[t-butoxycarbonyl]-5-indolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 113 mg (39%) of the title compound as an amorphous foam. FDMS: m/e = 445.  $\alpha[D]_{589} = +68.17$  (c = 0.47, chloroform).

40

analysis:	calculated	found
C	75.65	75.82
H	7.25	7.28
N	6.30	5.88

45

Example 251

(+)-(4aR)-(10bR)-4-methyl-8-(2-benzoxazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 45 mg (20%) of the title compound as an amorphous foam. FDMS: m/e = 346.

50

Example 252

(+)-(4aR)-(10bR)-4-methyl-8-(2-benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 107 mg (45%) of the title compound as an amorphous solid. mp: 207-212°. FDMS: m/e = 362.  $\alpha[D]_{589} = +88.83$  (c=0.60, chloroform).

analysis:	calculated	found
C	72.90	72.03
H	6.12	6.06
N	7.73	7.20

5

Example 253

10 (4aR)-(10bR)-4-methyl-8-(2-pyrazinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 132 mg (66%) of the title compound as an amorphous foam. FDMS: m/e = 308.  $\alpha[D]_{589} = +89.71$  (c=0.34, chloroform).

analysis:	calculated	found
C	74.24	73.97
H	6.89	6.55
N	13.67	13.50

Example 254

15 (4aR)-(10bR)-4-methyl-8-(2-pyrimidinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 102 mg (51%) of the title compound as an amorphous foam. mp 160-162°. FDMS: m/e = 307.  $\alpha[D]_{589} = +95.71$  (c=0.28, chloroform).

analysis:	calculated	found
C	74.24	73.29
H	6.89	6.88
N	13.67	13.52

25

30

Example 255

35 (4aR)-(10bR)-4-methyl-8-(2-quinoxaliny)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 156 mg (67%) of the title compound as a foam. mp 129-135°. FDMS: m/e = 357.  $\alpha[D]_{589} = +72.94$  (c=0.63, chloroform).

Example 256

40 (+)-4aR)-(10bR)-4-methyl-8-(2-benzimidazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 57 mg (25%) of the title compound as an amorphous foam. mp 183-186°. FDMS: m/e = 345.

analysis:	calculated	found
C	76.49	75.99
H	6.71	6.35
N	12.16	11.69

45

Example 257

50 (+)-4aR)-(10bR)-4-methyl-8-(3-indazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 49 mg (11%) of the title compound as an amorphous foam. FDMS: m/e = 345.

Example 258

55 (+)-4aR)-(10bR)-4-methyl-8-(2-[3-phenyl]tetrazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
 Yield: 69 mg (28%) of the title compound as an amorphous foam. mp 85-90°. FDMS: m/e = 373.  $\alpha[D]_{589} = +84.79$  (c=0.65, chloroform).

## EP 0 703 221 A1

analysis:	calculated	found
C	70.76	70.61
H	6.21	5.97
N	18.75	18.63

5

Example 259

10 (+)-(4aR)-(10bR)-4-methyl-8-(2-[5-trifluoromethyl]pyridinyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

Yield: 141 mg (58%) of the title compound as an amorphous foam. mp 65-68°. FDMS: m/e = 374.  $\alpha[D]_{589} = +81.90$  (c = 0.84, chloroform).

15

analysis:	calculated	found
C	67.37	67.12
H	5.65	5.68
N	7.48	7.23

20

Example 260

(+)-(4aR)-(10bR)-4-methyl-8-(2-naphtho<1,2-d>thiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

25 Yield: 192 mg (72%) of the title compound as an amorphous solid. mp 105-107°. FDMS: m/e = 412.  $\alpha[D]_{589} = +86.44$  (c=0.70, chloroform).

30

analysis:	calculated	found
C	75.70	75.46
H	5.86	5.58
N	6.79	6.55

Example 261

35 (+)-(4aR)-(10bR)-4-methyl-8-(2-[4-fluoro]benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

Yield: 181 mg (73%) of the title compound as an amorphous foam. mp 170-190°. FDMS: m/e = 380.  $\alpha[D]_{589} = +92.40$  (c=0.50, chloroform).

40

analysis:	calculated	found
C	69.45	69.68
H	5.56	5.80
N	7.36	7.07

45

Example 262

(+)-(4aR)-(10bR)-4-methyl-8-(2-[4-chloro]benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quino-  
lin-3-one

50 Yield: 177 mg (69%) of the title compound as an amorphous solid. mp 206-209°. m/e = 396.  $\alpha[D]_{589} = +91.10$  (c=0.81, chloroform).

55

analysis:	calculated	found
C	66.57	66.77
H	5.33	5.48
N	7.06	6.97

Example 263

(+)-(4aR)-(10bR)-4-methyl-8-(2-[5,6-dichloro]benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5 Yield: 113 mg (40%) of the title compound as an amorphous foam. FDMS: m/e = 431.  $\alpha[D]_{589} = +79.41$  (c=0.79, chloroform).

analysis:	calculated	found
C	61.26	60.99
H	4.67	4.82
N	6.49	6.31

Example 264

(+)-(4aR)-(10bR)-4-methyl-8-(2-[4-isopropyl]benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

15 Yield: 94 mg (36%) of the title compound as an amorphous solid. mp: 170-180°. FDMS: m/e = 404.

Example 265

(+)-(4aR)-(10bR)-4-methyl-8-(2-[6-chloro]benzothiazolyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

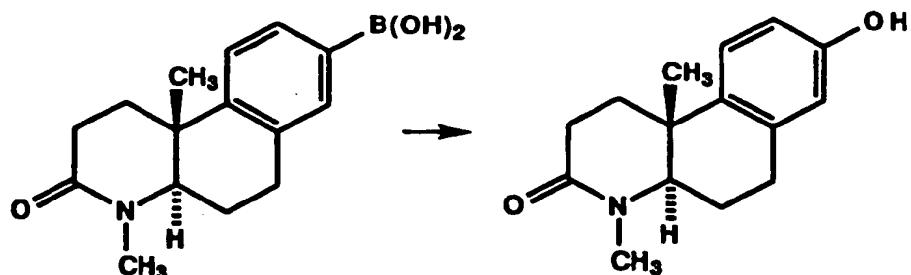
20 Yield: 100 mg (39%) of the title compound as a white solid. mp: 123-125°. FDMS: m/e = 396.  $\alpha[D]_{589} = +73.63$  (c=1.26, methanol).

analysis:	calculated	found
C	66.57	66.32
H	5.33	5.52
N	7.06	7.01

30 The following preparation and example illustrate the synthesis of compounds of the present invention wherein the X group is an oxygen atom.

Preparation 10

(+)-(4aR)-(10bR)-4-methyl-8-hydroxy-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



50 To a suspension of (+)-(4aR)-(10bR)-4-methyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one-8-boronic acid (1.0 g, 3.7 mmol) in 30 mL of THF was added 3 N sodium hydroxide (6 mL) followed by 6.0 mL of 30% hydrogen peroxide at -30°. The cold bath was removed, and the mixture was stirred at room temperature for 2.5 h. Six mL of saturated aqueous sodium sulfite solution was added, followed by 5 N hydrochloric acid until solution was acidic. Volatiles were removed via rotary evaporation, and the crude solid was heated in ethyl acetate and filtered to give 441 mg (53%) of the title compound as an amorphous solid. FDMS m/e = 245.

55

Example 266

(+)-(4aR)-(10bR)-4-methyl-8-(2-quinolinyloxy)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5

10

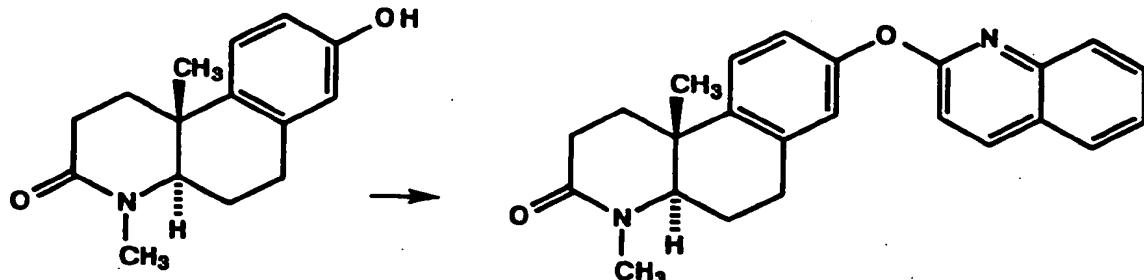
15

20

25

30

35



A 50 mL round bottom flask was charged with (+)-(4aR)-(10bR)-4-methyl-8-hydroxy-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (300 mg, 1.22 mmol), tetrabutylammonium chloride (339 mg, 1.22 mmol), 2-chloroquinoline (200 mg, 1.22 mmol), 4 mL of 50% sodium hydroxide solution, and 4 mL of toluene, fitted with a reflux condenser, and the stirred mixture was heated at 100°, under nitrogen, for 24 h. The mixture was cooled, diluted with water (50 mL) and extracted with chloroform (3 x 100 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (60% ethyl acetate/hexanes eluent; followed by an additional chromatography on a short silica column, eluting with 10% ethyl acetate/dichloromethane) to give 52 mg (11%) of the title compound as a white solid. mp 172-174°. FDMS: m/e = 372.  $\alpha_{D}^{25} = +67.74$  (c=0.43, chloroform).

analysis:	calculated	found
C	77.39	77.32
H	6.49	6.70
N	7.52	7.25

The following preparation and examples illustrate syntheses of compounds of the invention wherein the group X incorporates an amino group, and the synthesis uses a starting material having an amino substituent on the benzoquinolinone nucleus.

Preparation 11

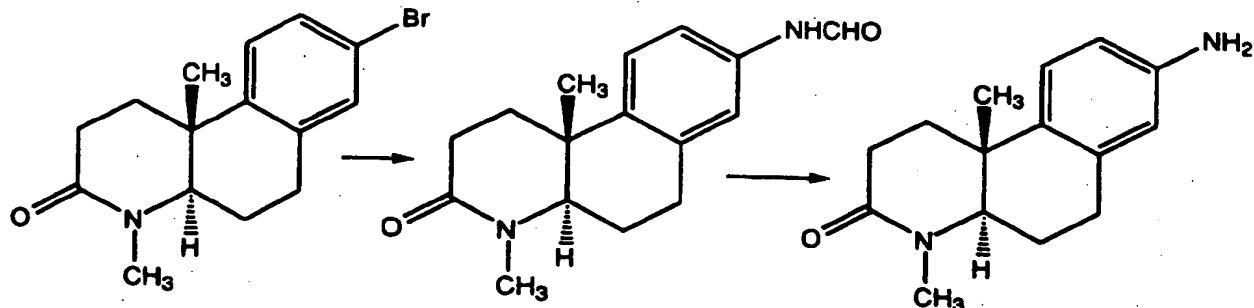
(4aR)-(10bR)-8-formamido-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one

40

45

50

55



In a sealable, heavy-walled pyrex tube equipped with teflon stirring bar was placed (4aR)-(10bR)-8-bromo-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one (500 mg, 1.6 mmol), copper(I) iodide (340 mg, 1.8 mmol), powdered potassium carbonate (500 mg, 3.6 mmol) and formamide (40 mL). The mixture was purged with nitrogen for 10 minutes and the tube sealed. The mixture was heated to 125° for 18 h. After cooling to ambient temperature, the tube was opened and the contents partitioned between water (250 mL) and ethyl acetate (250 mL). The aqueous phase was extracted with ethyl acetate (2X 100 mL) and the combined organic phase was dried over anhydrous magnesium sulfate and concentrated to afford crude 8-formamido intermediate product (220 mg) which was utilized without further purification. m/e 272.

The crude intermediate product was dissolved in ethyl acetate (50 mL), 5 N hydrochloric acid solution (10 mL) was

added and the solution stirred at ambient temperature for 2.5 h. The mixture was made basic with aqueous ammonium hydroxide solution and extracted with ethyl acetate (2 X 50 mL). The combined organic phase was dried over anhydrous magnesium sulfate and concentrated to afford crude product (90 mg) which was utilized without further purification. m/e 244.

5

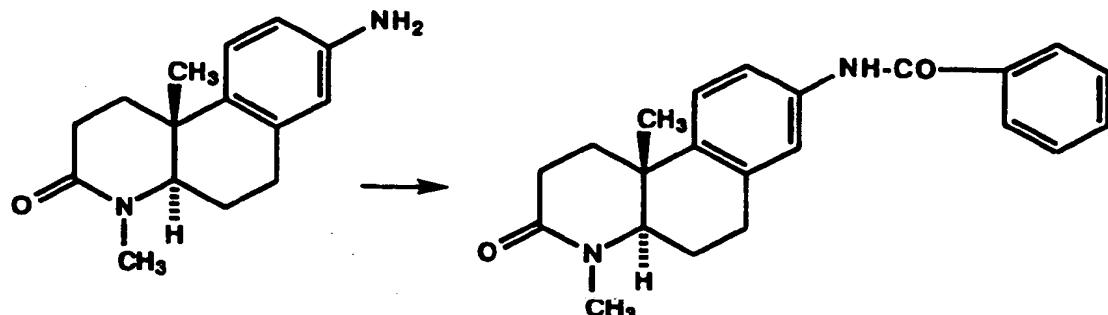
Example 267

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-benzoylamino-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

10

15

20



A 200 mg portion of (4aR)-(10bR)-4,10b-dimethyl-8-amino-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was dissolved in 50 mL of THF and a slight excess of benzoyl chloride was added. The mixture was stirred at ambient temperature for 3 h, and volatiles were then removed under vacuum. The resulting oil was triturated with diethyl ether,

25 and the resulting solids were purified by chromatography on silica gel, eluting with 50% methanol/ethyl acetate. A yield of 104 mg of solid product was obtained from the column and found to be the desired product, m.p. 220-222°. FDMS: m/e = 348.  $\alpha[D]_{589} = +75.53^\circ$

30

analysis:	calculated	found
C	75.83	75.62
H	6.94	6.97
N	8.04	7.98

35 The following examples were carried out according to the process of Example 267.

Example 268

(+)-(4aR)-(10bR)-4,10b-dimethyl-8-(3-nitrobenzoylamino)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

40 Yield: 595 mg of the desired product, m.p. 240-242°. FDMS: m/e = 393.  $\alpha[D]_{589} = +75.79^\circ$

45

analysis:	calculated	found
C	67.16	66.92
H	5.89	5.86
N	10.68	10.45

Example 269

50 (4aR)-(10bR)-4,10b-dimethyl-8-(4-nitrobenzoylamino)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

Yield: 38.2 mg of the desired product, m.p. 269-270°. FDMS: m/e = 393.

55

analysis:	calculated	found
C	67.16	66.88
H	5.89	5.82
N	10.68	10.59

## EP 0 703 221 A1

Example 270

(4aR)-(10bR)-4,10b-dimethyl-8-(3-aminobenzoylamino)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 80.5 mg of purified product, m.p. 154-156°. FDMS: m/e = 363.

analysis:	calculated	found
C	72.70	73.00
H	6.93	7.03
N	11.56	11.61

5

10

Example 271

(4aR)-(10bR)-4,10b-dimethyl-8-(4-aminobenzoylamino)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 30.6 mg of the desired product. FDMS: m/e = 363.

analysis:	calculated	found
C	66.07	65.84
H	6.55	6.72
N	10.51	10.46

20

Example 272

(+)-(4aR)-(10bR)-4-methyl-8-(3-diphenylmethylaminophenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 28 mg (83%) of the title compound as a white solid. mp 109-111°. FDMS: m/e = 486.  $\alpha[D]_{589} = +46.90$  (c = 0.49, methanol).

30

analysis:	calculated	found
C	83.91	83.62
H	7.04	7.14
N	5.76	5.51

35

Example 273

(+)-(4aR)-(10bR)-4-methyl-8-(3-[benzoylamino]phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one  
Yield: 50 mg (76%) of the title compound as an amorphous foam. mp 257-262° (decomp.) FDMS m/e = 424.  $\alpha[D]_{589} = +62.50$  (c = 0.61, chloroform).

analysis:	calculated	found
C	79.22	79.62
H	6.65	6.50
N	6.60	6.70

40

45

Example 274

50

(+)-(4aR)-(10bR)-4-methyl-8-(3-[pivaloylamino]phenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

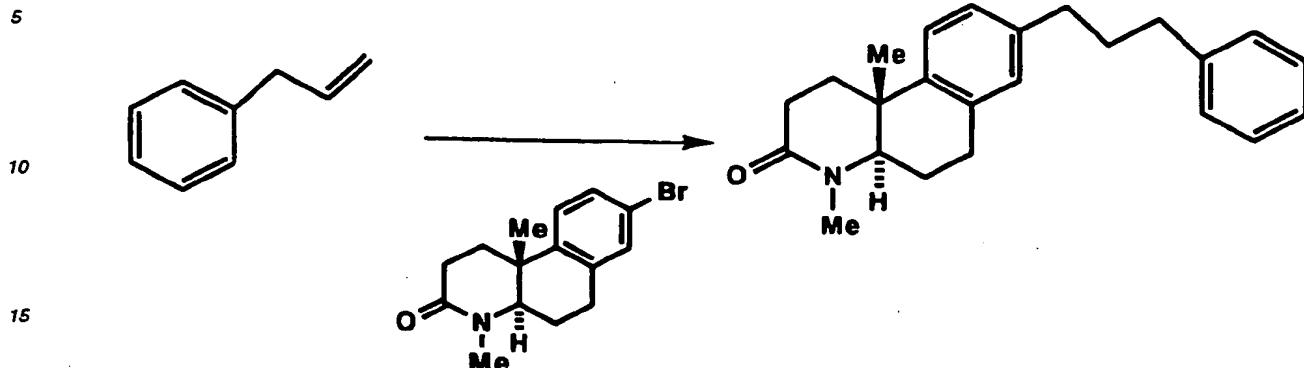
Yield: 25 mg (64%) of the title compound as a yellow solid. mp 95-98°. FDMS m/e = 404.  $\alpha[D]_{589} = +62.50$  (c = 0.16, chloroform).

55

The following group of examples demonstrates typical synthesis of compounds having X groups which are alkyl, alkenyl, and alkynyl.

Example 275

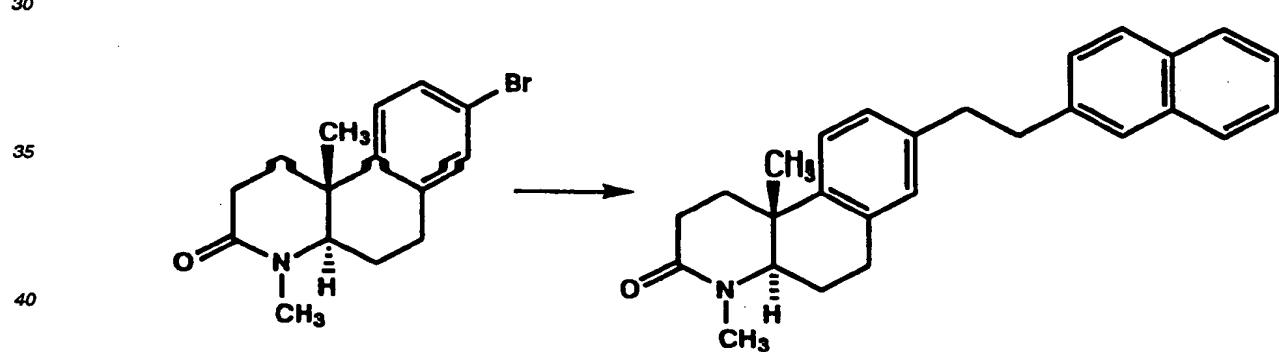
(+)-(4aR)-(10bR)-4-methyl-8-(3-phenylpropyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



To a solution of allylbenzene (106 mg, 0.89 mmol) in 0.5 mL of THF was added 9-BBN (0.89 mmol, 1 equiv) in THF, at 0°. Let stir for 1 h, warming to 5°. To the mixture was added (+)-(4aR)-(10bR)-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (250 mg, 0.812 mmol), triphenyl phosphine (42 mg, 0.16 equiv.), tetrakis(triphenylphosphine) palladium(0) (19 mg, 0.02 equiv.), 1 mL of 3 N sodium hydroxide solution and an additional 1 mL of THF. The resulting mixture was heated at 80° for 18 h, cooled, and ethanolamine was added, followed by ethyl acetate. The resulting organic phase was washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel chromatography (50-100% ethyl acetate / hexanes eluent gradient) to give 160 mg (59%) of the title compound as an oil. FDMS m/e = 347.

Example 276

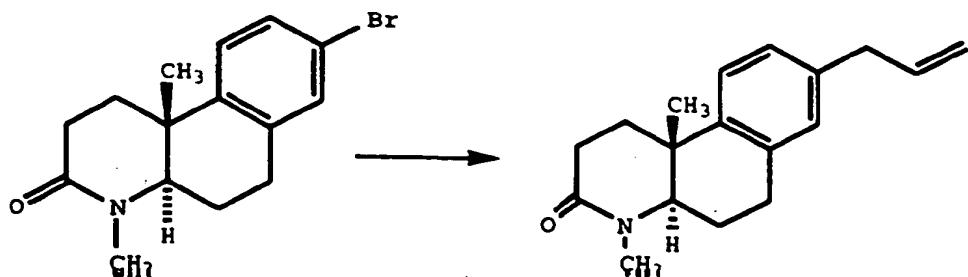
(+)-(4aR)-(10bR)-4-methyl-8-(2-[2-naphthyl]ethyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



To a solution of 2-vinylnaphthalene (138 mg, 0.89 mmol) in 0.5 mL of THF was added 9-BBN (0.89 mmol, 1 equiv) in THF, at 0°. Let stir for 1 h, warming to 5°. To the mixture was added (+)-(4aR)-(10bR)-4-H-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (250 mg, 0.812 mmol), triphenyl phosphine, (42 mg, 0.16 equiv.), tetrakis(triphenylphosphine) palladium(0) (19 mg, 0.02 equiv.), 1 mL of 3 N sodium hydroxide solution and an additional 1 mL of THF. The resulting mixture was heated at 80° for 18 h, cooled, and ethanolamine was added, followed by ethyl acetate. The resulting organic phase was washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel chromatography (50-100% ethyl acetate / hexanes eluent gradient) to give 186 mg (60%) of the title compound as a tan solid. mp 109-110°. FDMS m/e = 383.  $\alpha[D]_{589} = +46.45$  (c = 0.66, chloroform).

Preparation 12

(4aR)-(10bR)-4,10b-dimethyl-8-allyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



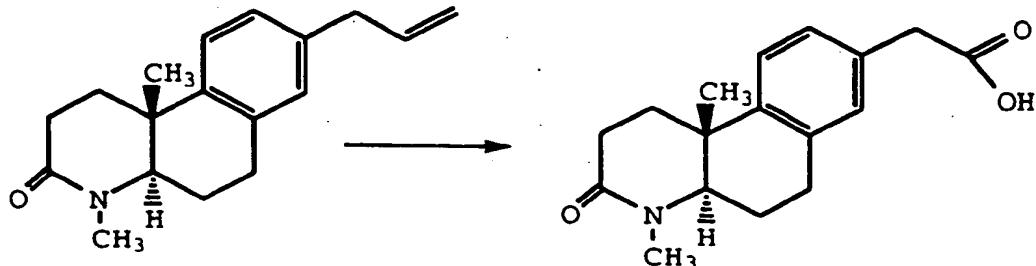
15 A 9 g portion of (4aR)-(10bR)-4,10b-dimethyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was combined with 11.1 g of tri-n-butyl-2-propenylstannane and 1.69 g of tetrakis(triphenylphosphine) palladium in 40 mL of acetonitrile in a sealable tube. Argon was bubbled through the mixture, the cap replaced, and the reaction heated at 90° for 18 h. Upon cooling, the mixture was filtered and the filtrate was concentrated under vacuum. The residue was triturated with diethyl ether to obtain 4.23 g of crystalline product, and a second crop of 1.31 g of product was also obtained. mp 144 -146°; FDMS 255 M+; Calcd for C<sub>17</sub>H<sub>21</sub>N<sub>1</sub>O<sub>2</sub>:

20

analysis:	calculated	found
C	79.96	79.69
H	8.29	8.22
N	5.49	5.73

25 Preparation 13

(4aR)-(10bR)-4,10b-dimethyl-8-carboxymethyl-1,2,3,4,4a,-5,6,10b-octahydrobenzo[f]quinolin-3-one



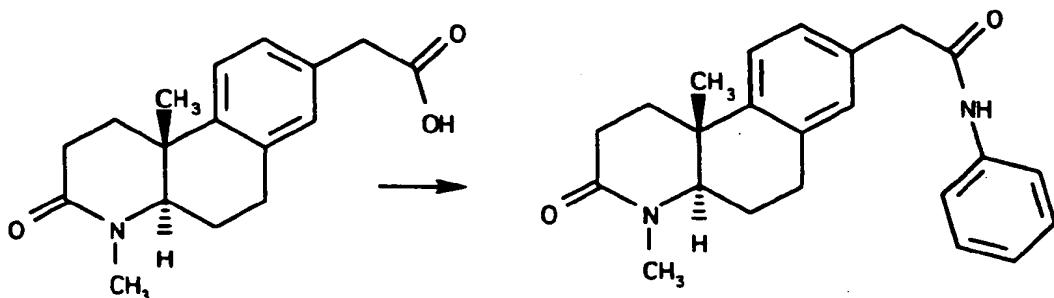
40 A 158 mg portion of the product of Preparation 12 was dissolved in 4 mL of acetonitrile, and a solution of 378 mg of sodium periodate in 4 mL of water was added, followed by 18 mg of ruthenium trichloride. The mixture was stirred at ambient temperature for 18 h, and diluted with dichloromethane. The organic layer was removed, and the aqueous layer extracted with dichloromethane. The organic layers were combined, washed with water, dried, filtered and evaporated to a brown foam. The residue was dissolved in dichloromethane and extracted with saturated aqueous sodium bicarbonate to which a few milliliters of 10% aqueous sodium carbonate had been added. The basic aqueous extract was made acid with hydrochloric acid, and extracted with dichloromethane. The organic layer was then dried and evaporated under vacuum to obtain 51 mg of a solid, which was recrystallized from ethyl acetate/hexane to obtain the desired product in purified form. mp: 200-202°;

45

analysis:	calculated	found
C	71.06	71.22
H	7.37	7.36
N	4.87	5.00

50 Example 277

55 (4aR)-(10bR)-4,10b-dimethyl-8-phenylaminocarbonylmethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

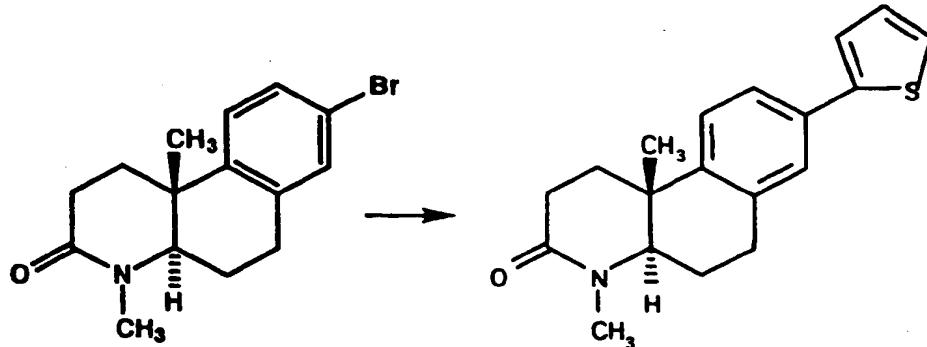


15 A 200 mg portion of the product of Preparation 13 was dissolved in 5 mL of dimethylformamide, and 135 mg of 1,1'-carbonyldiimidazole was added. The reaction mixture was blanketed with nitrogen, and was stirred at ambient temperature for 4 h, at which time 0.1 mL of aniline was added. The solution was then stirred briefly, and concentrated under vacuum. The residue was dissolved in dichloromethane and washed with 1N hydrochloric acid, 10% sodium sulfate, water and brine. The solution was then dried, filtered and evaporated to obtain 220 mg of crude product. It was purified by chromatography on a silica gel column, eluting with 3% isopropanol in chloroform. The product-containing fractions were combined, evaporated and recrystallized from ethyl acetate to obtain the desired product in pure form. mp 192-195°; 20 FDMS 362 M<sup>+</sup>.

analysis:	calculated	found
C	76.21	75.98
H	7.23	7.03
N	7.73	7.81

### Example 278

30 (4aR)-(10bR)-4,10b-dimethyl-8-(2-thiophenyl)-1,2,3,4,4a,-5,6,10b-octahydrobenzof]quinolin-3-one



45 Five hundred mg of (4aR)-(10bR)-4,10b-dimethyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was combined with 730 mg of 2-(tri-n-butylstannyl)thiophene and 100 mg of bis(triphenylphosphine) palladium chloride in 6 mL of acetonitrile in a screw capped sealable tube. The mixture was flushed with argon for 5 minutes, capped and heated at 90° for 20 h. Upon cooling, the mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by chromatography on a silica gel column, eluting with ethyl acetate, and the isolated product was recrystallized from ethyl acetate/hexane/chloroform to obtain 167 mg of the desired product. mp: 193-195°; FDMS 311.

analysis:	calculated	found
C	73.27	73.32
H	6.80	6.94
N	4.50	4.55

Example 279

(4aR)-(10bR)-4,10b-dimethyl-8-(2-phenylethenyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5

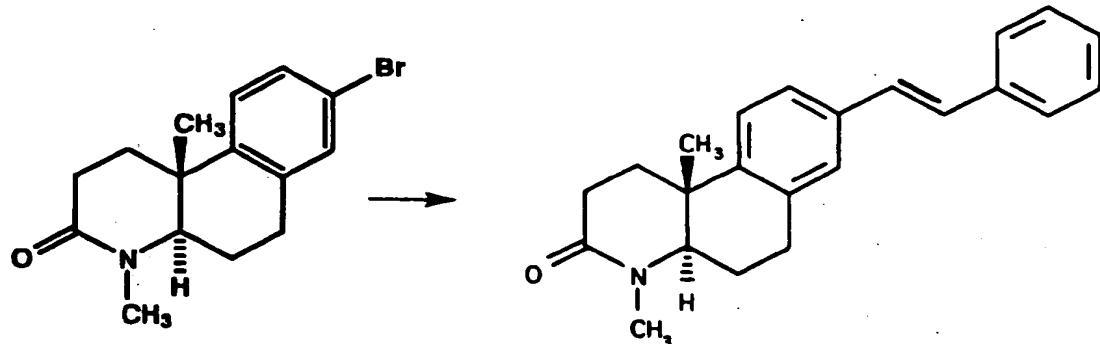
10

15

20

25

30



Five hundred mg of (4aR)-(10bR)-4,10b-dimethyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one, 4 mg of palladium acetate, 20 mg of tri-o-tolylphosphine, 0.34 mL of triethylamine and 5 mL of dimethylformamide were placed in a screw capped sealable tube with a stir bar. The mixture was warmed to 60° and then 200 mg of styrene was added and the vessel was flushed with argon. The vessel was then capped and heated at 120° for 24 h. The reaction mixture was cooled, diluted with ethyl acetate and filtered and the filtrate was concentrated under vacuum. The residue was dissolved in chloroform and washed twice with water. The organic layer was dried, filtered and evaporated under vacuum to obtain 400 mg of residue, which was recrystallized from ethyl acetate to obtain the desired product. m.p. 173-175°. FDMS m/e = 331.

analysis:	calculated	found
C	83.34	83.12
H	7.60	7.64
N	4.23	4.14

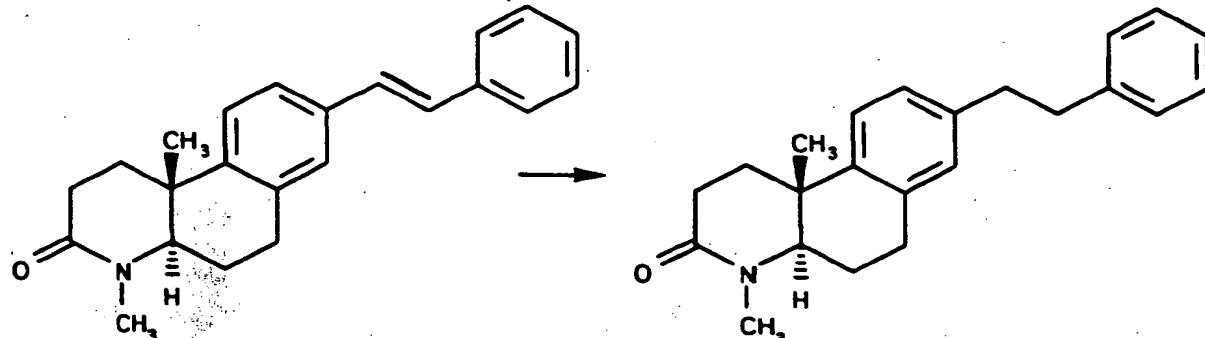
Example 280

(4aR)-(10bR)-4,10b-dimethyl-8-(2-phenylethyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

35

40

45



A 150 mg portion of the product of Example 279 was hydrogenated on a Parr apparatus at 40 p.s.i. in 50 mL of ethanol containing 5 mL of dimethylformamide and 20 mg of 10% palladium/carbon catalyst. When the starting material had been consumed, the mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by chromatography on silica gel, eluting with 90% ethyl acetate/hexane to obtain a product which was recrystallized from ethyl acetate/hexane to produce the desired product. m.p. 109-111°.

55

analysis:	calculated	found
C	82.84	83.02
H	8.16	8.10
N	4.20	4.06

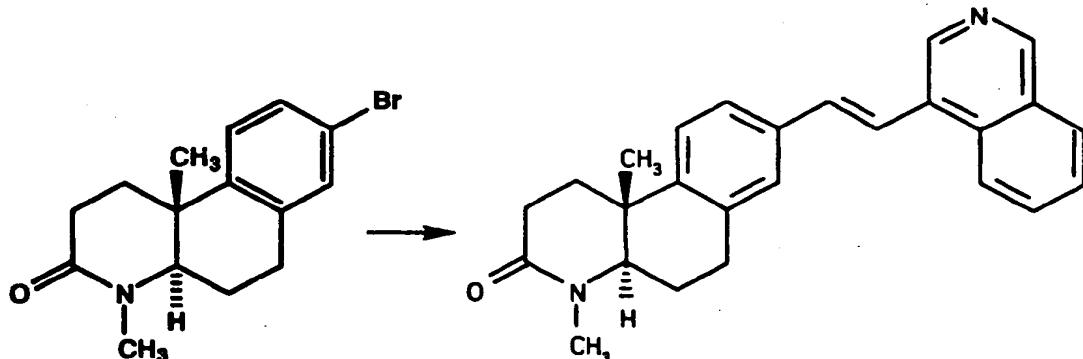
Example 281

(4aR)-(10bR)-4,10b-dimethyl-8-(2-[4-isoquinoliny]ethenyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5

10

15



A 508 mg portion of (4aR)-(10bR)-4,10b-dimethyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one, 4 mg of palladium acetate, 20 mg of tri-*o*-tolylphosphine, 0.34 mL of triethylamine and 5 mL of dimethylformamide were combined in a sealable tube with a stir bar, and the mixture was warmed to 50° under argon. An 0.26 g portion of 4-ethenylisoquinoline was added. Then the vessel was blanketed with argon and sealed and the mixture was heated with stirring at 120° for 20 hours. It was then cooled, and concentrated under vacuum and the residue was purified by chromatography on silica gel, eluting with 5% isopropanol in chloroform. An 0.29 g portion of an oil was obtained, which was recrystallized from ethyl acetate/hexane to obtain the desired product in crystalline form. mp 183-185°; FDMS 382 M+.

25

30

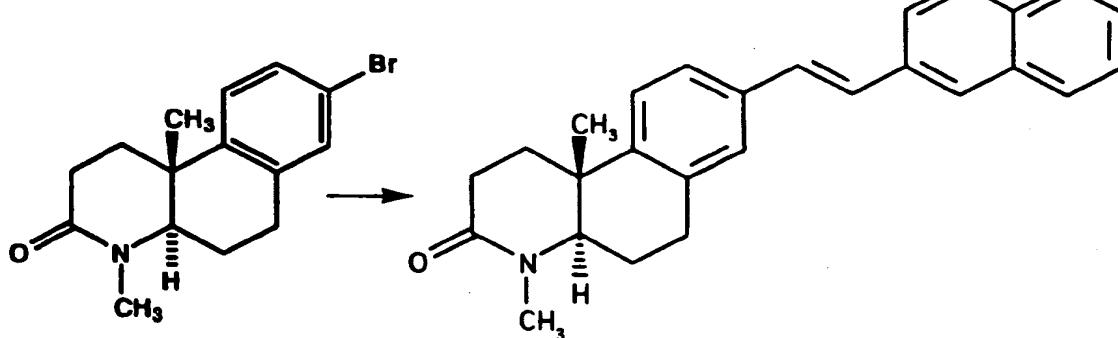
analysis:	calculated	found
C	81.64	81.43
H	6.85	6.94
N	7.32	7.22

Example 282

35 (4aR)-(10bR)-4,10b-dimethyl-8-(2-[3-quinoliny]ethenyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

40

45



50

A 290 mg portion of 3-ethenylquinoline was used in a process otherwise similar to that of Example 281 to obtain the title product. mp 181-183°; FDMS 382.

55

analysis:	calculated	found
C	81.64	81.89
H	6.85	6.71
N	7.32	7.55

Example 283

(4aR)-(10bR)-4,10b-dimethyl-8-(2-quinolinyloxy)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

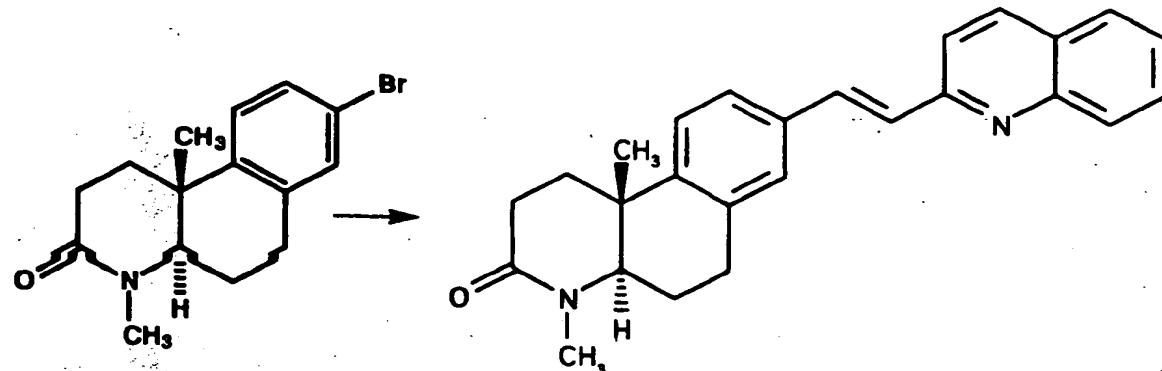
5

10

15

20

25



The process of Example 281 was substantially repeated, using 0.34 g of 2-ethenylquinoline as the starting material to obtain the title product. mp 233-236°; FDMS 382.

analysis:	calculated	found
C	81.64	81.42
H	6.85	7.00
N	7.32	7.57

Example 284

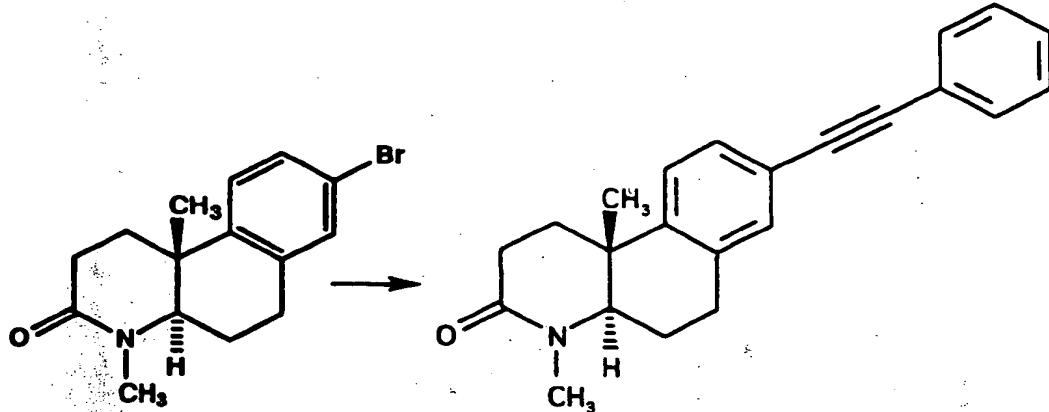
(4aR)-(10bR)-4,10b-dimethyl-8-(2-phenylethynyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

30

35

40

45



A 1 g portion of (4aR)-(10bR)-4,10b-dimethyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one was reacted with 0.4 mL of phenylacetylene in a process substantially similar to that of Example 281 to obtain the desired title product in pure form: mp 205-208°; FDMS 329.

50

55

analysis:	calculated	found
C	83.85	84.07
H	7.04	7.05
N	4.25	4.27

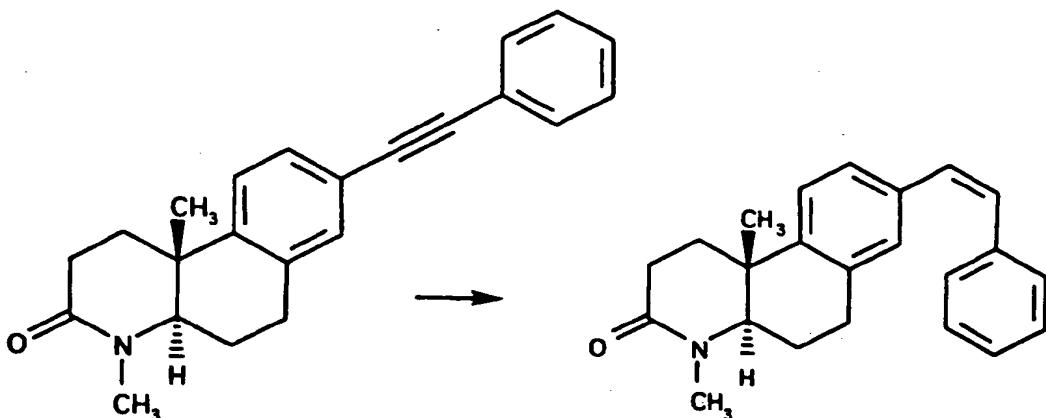
Example 285

(4aR)-(10bR)-4,10b-dimethyl-8-(2-phenylethynyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5

10

15



A 300 mg portion of the product of Example 284 was hydrogenated over palladium/barium sulfate catalyst in 25 mL of pyridine at 15 psi hydrogen pressure at ambient temperature for 1 h. The mixture was then filtered and concentrated under vacuum, and the residue was purified by chromatography on silica gel, eluting with 75 % ethyl acetate/hexane. The product thereby obtained was further purified on a Chromatotron, eluting with 5% isopropanol in chloroform to obtain the desired product in the form of a yellow oil. High resolution mass spectroscopy showed the correct molecular ion of 332.201440.

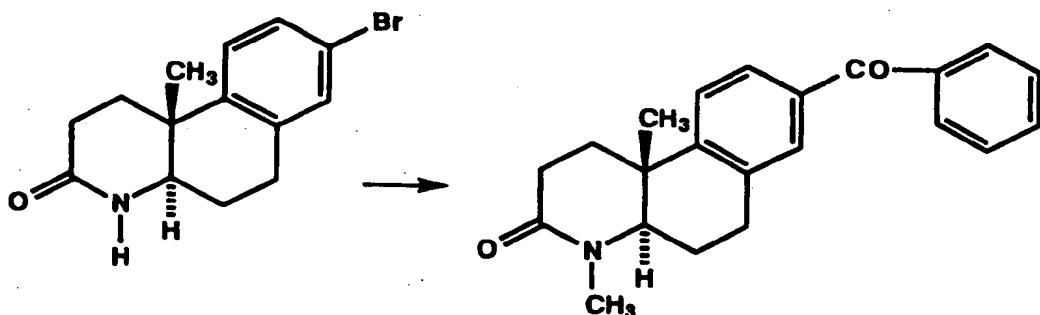
Example 286

25

(4aR)-(10bR)-8-benzoyl-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

30

35



40

45

50

A. To a solution of (4aR)-(10bR)-10b-methyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one in 25 mL of THF at -78° under an atmosphere of nitrogen was added 330 µL of a 1.4 M solution of methylolithium in diethyl ether (0.46 mmol). The reaction mixture turned bright yellow, and after 10 min, 470 µL of a 1.7 M solution of t-butyl-lithium in pentane (0.80 mmol) was added. The reaction mixture was stirred for 10 min before the addition of benzaldehyde (80 µL, 0.79 mmol) as a single aliquot. The reaction was warmed to room temperature and stirred for 30 min before partitioning between diethyl ether and 1N hydrochloric acid. The ether layer was dried over sodium sulfate, filtered and evaporated under reduced pressure to afford 0.1818 g crude product. The material was purified on a Chromatotron (2mm plate, dry loaded with chloroform, eluted with 5% methanol/chloroform) to give 106 mg of desired product. A portion of this material was triturated with diethyl ether to yield a white solid. mp 116-118; FDMS: m/e = 321.  $\alpha$ [D]<sub>589</sub> = 100.39

55

analysis:	calculated	found
C	78.47	78.45
H	7.21	7.26
N	4.36	4.21

B. To a solution of the alcohol prepared as described above (395 mg, 1.2 mmol) in 40 mL of acetone at 0° was added dropwise 1 mL (2.54 mmol) of a 2.54 M solution of Jones Reagent. The reaction mixture was stirred at 0°

for 15 min. before the addition of 2 mL of isopropanol to quench the excess reagent. The mixture was partitioned between ethyl acetate and brine. The aqueous layer was extracted with chloroform. The combined organic layers were washed with water (100 mL), dried (sodium sulfate), filtered and evaporated under reduced pressure to afford crude product. This material was purified on a chromatotron (2mm plate, dry loaded with chloroform, eluted with 5% methanol/chloroform) to give 166 mg of desired product (42% yield). This material was methylated using the standard potassium t-butoxide/methyl iodide in t-butanol method to afford 170 mg crude product. This material was purified on a chromatotron (2mm plate, eluted with ethyl acetate) to give 113 mg of desired white solid (65% yield); mp 173-175°; FDMS: m/e=334;  $\alpha[D]_{589} = 80.39$  (c=0.5 in chloroform).

5

10

analysis:	calculated	found
C	79.25	79.49
H	6.95	7.07
N	4.20	4.30

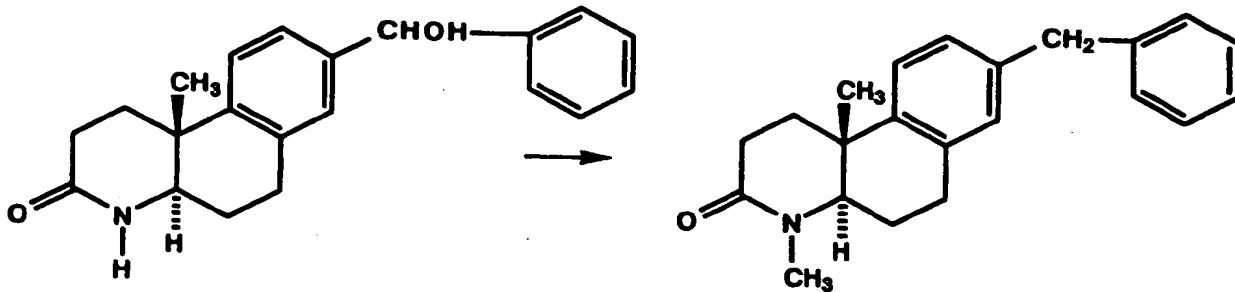
15

### Example 287

(4aR)-(10bR)-8-benzyl-4,10b-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

20

25



30

35

40

45

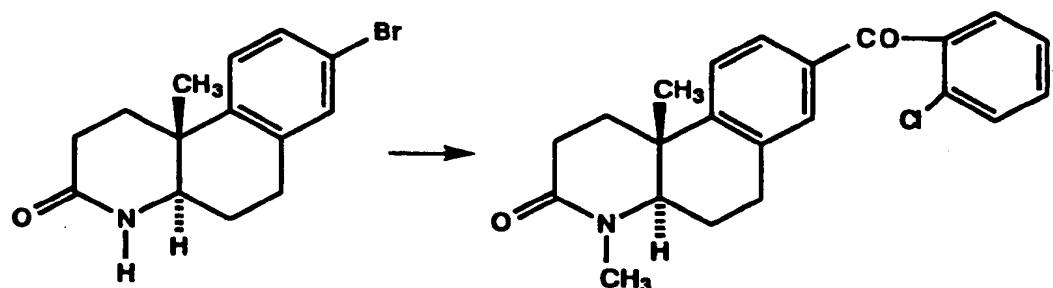
analysis:	calculated	found
C	82.72	82.68
H	7.89	7.87
N	4.38	4.33

### Example 288

(4aR)-(10bR)-8-(2-chlorobenzoyl)-4,10b-dimethyl-1,2,3,4,4a,-5,6,10b-octahydrobenzo[f]quinolin-3-one

50

55



5 To a solution of (4aR)-(10bR)-10b-methyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one in 50 mL of THF at -78° under an atmosphere of nitrogen was added 2.25 mL of a 1.4 M solution of methylolithium in diethyl ether (3.15 mmol). After 10 min, 3.34 mL of a 1.7 M solution of t-butyllithium in pentane (5.68 mmol) was added. The reaction mixture was stirred for 10 min before the addition of 2-chlorobenzaldehyde (870 mL, 7.72 mmol) as a single aliquot. The reaction was warmed to room temperature and stirred for 2 h before partitioning between ethyl acetate and 1N hydrochloric acid. The organic layer was dried, filtered and evaporated under reduced pressure to afford 1.7 g of crude product. The material was purified on a Chromatotron (4 mm plate, dry loaded with chloroform, eluted with 5% methanol/chloroform) to give 435.5 mg of desired product (47% yield); mp 105-115°; FDMS: m/e = 355, 357.

20

analysis:	calculated	found
C	70.88	70.87
H	6.23	6.25
N	3.94	3.92

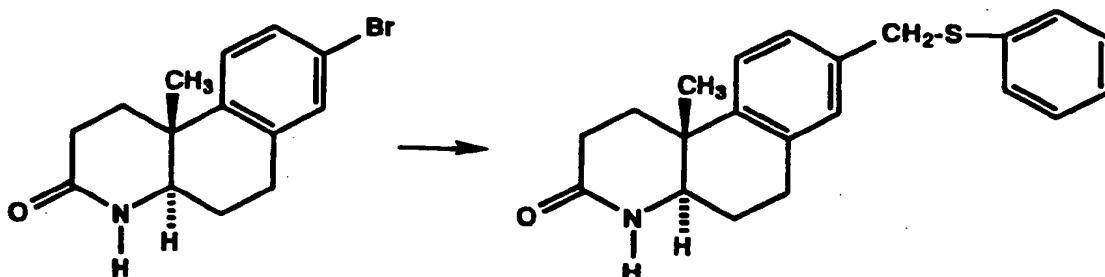
25

To a solution of the alcohol prepared as described above (211.7 mg, 0.6 mmol) in 25 mL of acetone at 0° was added dropwise 0.5 mL (1.27 mmol) of a 2.54 M solution of Jones Reagent. The reaction mixture was stirred at 0° for 30 min before the addition of 2 mL of isopropanol to quench the excess reagent. The mixture was partitioned between chloroform and brine. The organic layer was dried, filtered and evaporated under reduced pressure to afford crude product. This material was purified on a Chromatotron (2mm plate, dry loaded with chloroform, eluted with 5% methanol/chloroform to give 81.0 mg of desired product.

This material was methylated using the standard potassium t-butoxide/methyl iodide in t-butanol method to afford 160 mg crude product. This material was purified on a Chromatotron (2mm plate, eluted with 2% methanol/ethyl acetate) followed by a second Chromatotron run (2mm plate, eluted with 5% methanol/chloroform) to give 61 mg of white foam after concentration from diethyl ether (65% yield); mp 65-70°.

#### Example 289

40 (4aR)-(10bR)-8-phenylthiomethyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one



45 A. To a solution of (4aR)-(10bR)-10b-methyl-8-bromo-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one in 60 mL of THF at -78° under an atmosphere of nitrogen was added 2.9 mL of a 1.4 M solution of methylolithium in diethyl ether (4.1 mmol). After 20 min, 4.8 mL of a 1.7 M solution of t-butyllithium in pentane (8.2 mmol) was added. The reaction mixture was stirred for 45 min before the addition of dimethylformamide (0.63 mL, 8.1 mmol). The reaction was warmed to room temperature before partitioning between ethyl acetate and 1N hydrochloric acid. The organic

layer was washed with additional 1 N hydrochloric acid, saturated sodium bicarbonate, brine and then dried (sodium sulfate), filtered and evaporated under reduced pressure to afford 665 mg desired product (80% crude yield). This material was taken on without further purification.

5 B. To a solution of the aldehyde prepared above (665 mg, 2.73 mmol) in 50 mL of absolute ethanol was added 2 equivalents of sodium borohydride (207 mg, 5.4 mmol). The reaction mixture was stirred at room temperature for 18 h before the addition of 50 mL of 1N hydrochloric acid. After stirring for 1.5 h, ethyl acetate was added and the material concentrated to remove ethanol. The residual aqueous layer was extracted with ethyl acetate and the organic layer was washed with brine, dried (sodium sulfate), and concentrated under reduced pressure to afford 10 436 mg of crude product. This material was purified on a Chromatotron (eluted with 3% methanol/chloroform) to give 310 mg of desired white solid (46 % yield): mp 176-177 °; FDMS: m/e = 245;  $\alpha[D]_{589} = 120.08$  (c = 0.5 in methanol).

analysis:	calculated	found
C	73.44	73.73
H	7.81	7.96
N	5.71	5.82

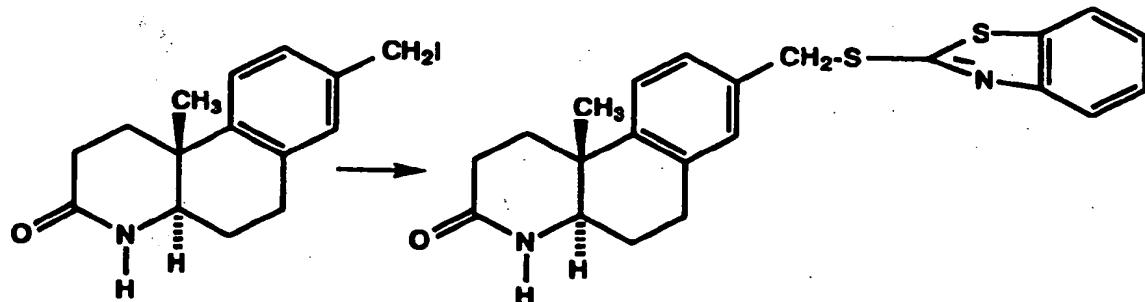
20 C. To a solution of the alcohol prepared as described above (462.3 mg, 1.88 mmol) in 40 mL of anhydrous acetonitrile was added 0.8 mL of neat trimethylsilyl iodide (5.6 mmol). After 30 minutes, the reaction mixture was concentrated and the residue partitioned between ethyl acetate and saturated thiosulfate. The organic layer was washed with brine, dried (sodium sulfate) and concentrated under reduced pressure to yield 664 mg of crude product. This material was purified on a Chromatotron (4 mm plate, eluted with 3% methanol/chloroform) to give 597 mg of desired 25 solid (89 % yield): mp 215-217 °; FDMS: m/e = 355, 228 (m - 1);  $\alpha[D]_{589} = 99.12$  (c = 0.5 in methanol). Material was taken on without further purification.

30 D. To a solution of the iodide prepared as described above (249.4 mg, 0.70 mmol) in 25 mL of THF was added a solution of 145  $\mu$ L of phenylmercaptan (1.4 mmol) and 210  $\mu$ L of DBU (???) (1.4 mmol) in 5 mL of THF. After stirring at room temperature for 2 days, the reaction mixture was partitioned between 1N hydrochloric acid and ethyl acetate. The organic layer was washed sequentially with 1N hydrochloric acid, 1N sodium hydroxide, and brine before being dried (sodium sulfate) and concentrated under reduced pressure to yield 293 mg of crude product. This material was purified on a Chromatotron (4 mm plate, eluted with 3% methanol/chloroform) followed by recrystallization from 35 ethyl acetate to give 166 mg of desired white solid (70% yield): mp 187-189°; FDMS: m/e = 337;  $\alpha[D]_{589} = 82.27$  (c = 0.5 in methanol).

analysis:	calculated	found
C	74.74	74.97
H	6.87	7.11
N	4.15	4.29

#### Example 290

45 (4aR)-(10bR)-8-(2-benzothiazolyl)thiomethyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

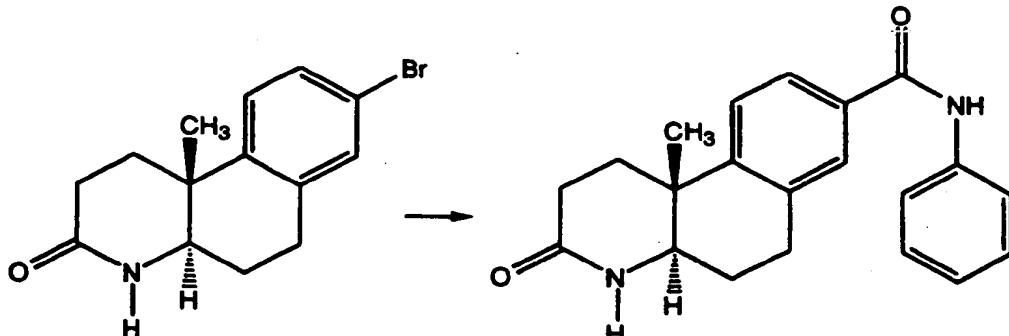


To a solution of the iodomethyl compound prepared in Step C of Example 289 in 25 mL of THF was added a solution of 252 mg of 2-mercaptopbenzothiazole (1.5 mmol) and 226 mL of diazabicycloundecane (DBU) (1.5 mmol) in 5 mL of THF. After stirring at room temperature for 2 days, the reaction mixture was partitioned between 1N hydrochloric acid and ethyl acetate. The organic layer was washed sequentially with 1N hydrochloric acid, 1N sodium hydroxide, and brine before being dried (sodium sulfate) and concentrated under reduced pressure to yield 382 mg of crude product. This material was purified on a Chromatotron (4 mm plate, eluted with 3% methanol/chloroform) followed by recrystallization from ethyl acetate to give 193 mg of desired white solid. mp 201-202°. FDMS: m/e = 394.  $\alpha[D]_{589} = 75.70$

analysis:	calculated	found
C	66.97	67.23
H	5.62	5.82
N	7.10	7.22

15 Example 291

(+)-(4aR)-(10bR)-8-phenylcarboxamido-10b-methyl-1,2,3,4,4a,-5,6,10b-octahydrobenzo[f]quinoline-3-one



In a flame-dried 3-neck round bottom flask equipped with magnetic stirrer and nitrogen inlet was dissolved (4aR)-(10bR)-8-bromo-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-3-one (500 mg, 1.7 mmol), in anhydrous THF (50 mL). The solution was cooled to -78° and treated with ethereal methylolithium (1.3 mL, 1.4M, 1.8 mmol) added dropwise over 2 min. After further stirring for 15 min., a solution of *t*-butyllithium (2.1 mL, 1.7 M in pentane, 3.6 mmol) was added dropwise. Following complete addition, the suspension was treated with phenylisocyanate (418  $\mu$ L, 3.6 mmol) in a single portion. The mixture was warmed to ambient temperature and acidified with 1 N hydrochloric acid solution. The mixture was extracted with ethyl acetate and the organic phase washed with brine and dried over anhydrous magnesium sulfate. Removal of solvent and chromatography of the crude product on silica gel (0.5% aqueous ammonium hydroxide/ethyl acetate as eluent) and crystallization from ethyl acetate afforded product as tan solid. m/e 334, OR (c=1.0, MeOH) @589 nm, +100.1°, @365 nm, +308.4°.

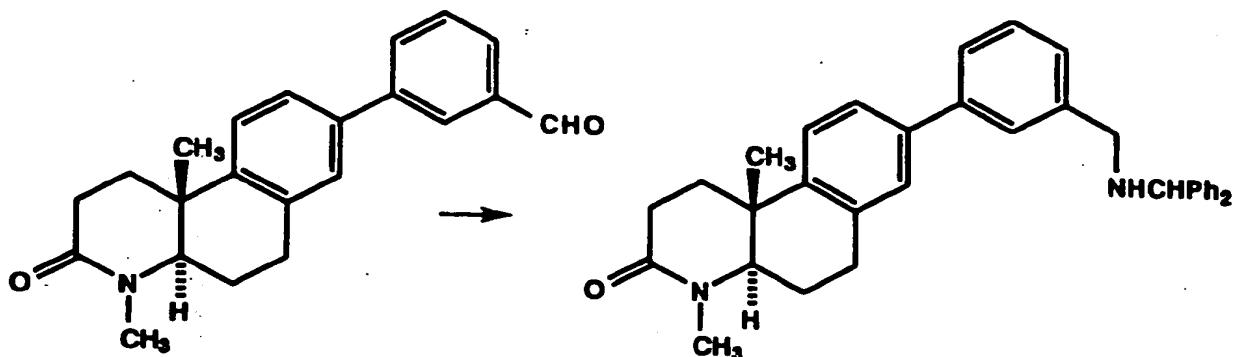
analysis:	calculated	found
C	75.42	75.22
H	6.63	6.76
N	8.38	8.25

45 Example 292

50 (+)-(4aR)-(10bR)-4-methyl-8-(3-diphenylmethylamino-methylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one

5

10



To a suspension of (+)-(4aR)-(10bR)-4-methyl-8-(3-formylphenyl)-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one (30 mg, 0.09 mmol), in 0.75 mL of methanol was added benzhydryl amine (0.09 mmol), sodium cyanoborohydride (0.09 mmol) and 2 drops of glacial acetic acid (mixture became homogeneous; pH = 4). The reaction was stirred at room temperature for 60 h. The mixture was diluted with ethyl acetate, saturated aqueous sodium bicarbonate solution was added, and the resulting mixture was extracted repeatedly with ethyl acetate. The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (ethyl acetate eluent), followed by trituration of the resulting oil with ether / hexanes, to give 36 mg (80%) of the title compound as a white solid. mp 55-57°. FDMS: m/e = 500.  $\alpha[D]_{589} = +48.40$  (c = 0.64, methanol).

25

analysis:	calculated	found
C	83.96	83.42
H	7.25	6.92
N	5.60	5.62

30

### Biological Testing

35

Representative compounds of the present invention have been tested in standardized biological test methods in order to determine their activity as inhibitors of both Type I and Type II 5AR. The following test methods are adapted to routine use and may be followed conveniently by the skilled reader.

40

### Methodology of Human Type I and Type II Steroid 5 $\alpha$ -Reductase Assays

#### Preparation of Type I 5 $\alpha$ -Reductase from Human Scalp:

45

Scalp punch biopsies from graft recipient sites were obtained from human hair transplant procedures immediately after surgery and were frozen on dry ice and stored at -80°C. Approximately 60-75 punches from one surgical procedure were used to generate an enzyme preparation. The subcutaneous tissue was cut away and discarded. The skin was frozen with liquid nitrogen and pulverized to powder. The powder was homogenized in 30 mL of ice-cold buffer (20 mM Tris-HCl, pH 7.5) using a Brinkmann Polytron (Westbury, NY) with a PTA 10-S probe and a setting of 7. The homogenization procedure consisted of four 15 second pulses. Connective tissue was cleared from the probe with forceps between pulses. The homogenate was then filtered through cheese cloth and the filtrate centrifuged at 100,000 x g for one hour in a Beckman L8-60M ultracentrifuge. The pellet was resuspended by homogenization with a Dounce homogenizer using the same buffer solution. An aliquot was taken for protein determination by the Lowry method, Lowry, *et al.*, Protein Measurement with the Folin Phenol Reagent, *J. Biol. Chem.*, 193, 265-75 (1951). Aliquots of the enzyme preparation were stored at -80° until use.

50

#### Preparation of Type II 5 $\alpha$ -Reductase from Human Prostate:

55

The same procedure as above was used for preparations using tissue from prostate surgery with the following changes: The buffer used was 20 mM sodium phosphate, pH 6.5; and the pellet was resuspended in the sodium phosphate buffer containing 20% glycerol.

**Human 5 $\alpha$ -R ductase Assay:**

This enzyme assay is based on the conversion of [<sup>3</sup>H]-testosterone to [<sup>3</sup>H]-5 $\alpha$ -dihydrotestosterone (DHT) and other 5 $\alpha$ -reduced metabolites. While about 90% of the 5 $\alpha$ -reduced metabolites formed in these assays was DHT, androstanedione was formed at about 10%. Essentially no androsterone was detected. In a total volume of 1.0 mL, the Type I assay contained 2.6  $\mu$ Ci [<sup>3</sup>H]-testosterone (50 nM), 500  $\mu$ M of reduced nicotine adenine dinucleotide phosphate, 100 mM Tris-HCl, pH 7.5, (in Type II assays, 40 mM sodium acetate at pH 5.5 is used instead of Tris-HCl) and test compounds as indicated. Test compounds were added in 20  $\mu$ L of dimethylsulfoxide (20  $\mu$ L of dimethylsulfoxide was added to blanks and controls). The reaction was initiated by the addition of 0.5 mg of Type I or Type II 5 $\alpha$ -reductase. The reaction mixture was incubated at 25° for 30 min in Type II assays, or 180 min in Type I assays, and terminated by the addition of 1 mL ice-cold stopping solution. The stopping solution contained 40  $\mu$ M each of non-radioactive testosterone, DHT, androstanedione, androstanedione, androsterone, androstan-3 $\beta$ , 17 $\beta$ -diol, and androstan-3 $\alpha$ , 17 $\beta$ -diol.

The samples were prepared for high performance liquid chromatography by solid phase extraction. Disposable solid matrix extraction columns (C-18 reversed phase, 6 mL, 500 mg; Bond Elut™ from Analytichem International; Harbor City, CA) were conditioned by washing with 5 mL of methanol followed by 5 mL of deionized water. The reaction mixtures were then applied to the columns. The columns were subsequently washed with 5 mL of acetone:water (1:4), followed by 0.3 mL of methanol. The samples were then eluted with 3 mL of methanol and collected in 20 mL scintillation vials. Three mL of water was then added to each scintillation vial. The solutions were then transferred to tubes and centrifuged for 30 min at 1000 x g to remove any particulate material before chromatography.

The [<sup>3</sup>H]-testosterone substrate and its metabolites were separated by chromatography using a C-18 reversed phase column (Beckman Ultrasphere 5 $\mu$ m spherical 80A pore, part no. 235329, 4.6 mm i.d. x 25 mm length) with an isocratic mobile phase (46 water: 46 methanol: 8 tetrahydrofuran by volume). The column temperature was maintained at 35° and the flow rate was 1.5 mL/min. A 400  $\mu$ L aliquot was injected onto the column and radioactivity was determined using a Beckman 171 in-line flow radioisotope detector in conjunction with Rainin Dynamax™ software and a Macintosh computer. The flow rate of the Atomflow™ scintillation fluid was 4.5 mL / min.

While in most instances the compounds listed below have been tested at various concentrations, only the test results at 0.3  $\mu$ M concentration are shown here, in order to reduce the bulk of the following table. The data are reported as percent inhibition of Type I and Type II AR produced by each compound at that concentration, compared to control reaction mixtures.

30

35

40

45

50

55

Table I

5

Compound of Example No.	Type I	Type II
10		
5	44	0
6	11	23
7	49	42
8	22	59
9	3	31
10	22	40
11	87	40
12	16	22
13	11	22
14	37	25
15	23	39
16	14	28
17	29	19
18	7	15
19	59	56
20	22	48
21	27	42
22	-	19
23	59	31
24	88	28
25	83	31
26	86	46, -2, 33
27	92	58, 1, 50
28	65	36
29	78	26
30	19	21
31	84	22
32	71	18
33	55	40
34	13	5
35	17	27
36	41	52
37	72	58
38	84	56, 38
39	81	34
40	90	35
41	88	18
42	-	32
43	68	18
44	-	27
45	11	45
46	3	31
47	-	16
48	-	12
49	96	4
50	95, 94	32

	51	91	14
	52	68	10
	53	100, 66	41
5	54	-	22
	55	68	11
	56	92	3
	57	-	20
	58	65	24
10	59	-	31
	60	-	42
	61	53	36
	62	45	42
	63	-	19
15	64	81	22
	65	79	42
	66	67	33
	67	22	54
	68	31	37
20	69	84	6
	70	-	36
	71	80	47
	72	16	26
	73	87	16
25	74	16	26
	75	63	40
	76	83	46
	77	88	46, 33
	78	-	3
30	79	-	34
	80	76	29
	81	92	25
	82	85	31
	83	-	12
35	84	88	23
	85	-	12
	86	66	51
	87	83	28
	88	96	43
40	89	-	15
	90	-	22
	91	87	32
	92	-	10
	93	-	9
45	94	-	1
	95	95	35
	96	89	52
	97	-	-
	98	76	61, 44
	99	88	65, 29
50	100	96	51, 34
	101	75	43
	102	92	61
	103	81	58
	104	89	41
55	105	92	33

## EP 0 703 221 A1

106	73	39
107	80	83
108	100	29
5	97	25
109	97	73
110	44	38
111	64	90, 92
112	70	51
113	55	47
10	31	20
114	-	24
115	46	49
116	25	43
117	84	59, 24
118	93	37
15	-	41
119	10	36
120	23	27
121	64	32
122	85	36
20	-	43
123	82	40
124	91	40
125	83	36
126	57	29
127	87	44
25	77	24
128	97	34
129	92	46
130	100	31
131	90	32
132	88	37
30	77	26
133	30	59
134	-	20
135	22	19
136	63	40
137	90	18
138	85	40
35	88	41
139	13	32
140	35	83, 83
141	-	12
142	2	33
40	22	69
143	63	28
144	90	10
145	85	71
146	13	25
45	35	60
147	31	70
148	47	79
149	49	63
150	56	87, 83
45	58	38
151	67	
152	31	
153	47	
50	49	
154	56	
155	58	
156	71	
157	88	
158	78	
55	87, 87	
159	61	
160		

	161	71	51
5	162	79	87
	163	80	86
	164	85, 87	86, 85, 79
	165	61	74
	166	50	49
	167	62	31
10	168	85	41
	169	75	61
	170		
	171	43	63
	172	55	36
15	173	65	78, 77
	174	82	80
	175	58	40
	176	25	15
	177	58	15
20	178		
	179	61	28
	180	59	30
	181	63	31
	182	63	100
25	183	89	88, 87
	184	73	81
	185	88	90
	186	90	79
	187	93	94
30	188	88	78
	189	84	19
	190	76	26
	191	65	19, 28
	192	80	33
35	193	-	-
	194	-	-
	195	90	71
	196	11	45
	197	-	37
40	198	-	7
	199	-	30
	200	59	72, 64
	201	69	60, 57
	202	41	48
45	203	8	34
	204	34	39
	205	100	37
	206	97, 100	32
	207	45	16
	208	77	10
50	209	24	11
	210	81	38
	211	70	29
	212	73	31
55	213	64	28
	214	26	29
	215	84	42

5	216	78	24
	217	93	33
	218	84	35
	219	91	30
	220	67	26
	221	95	26
	222	86	27
	223	36	24
10	224	71	20
	225	47	32
	226	16	8
	227	97	25
	228	77	32
15	229	97	11
	230	86	29
	231	80	21
	232	94	27
	233	95	38
20	234	83	30
	235	28	12
	236	84	67
	237	33	13
	238	72	29
25	239	42	27
	240	55	17
	241	65	33
	242	5	24
	243	88	54
30	244	51	32
	245	54	44
	246	92	45
	247	60	32
	248	54	22
35	249	69	24
	250	83	1
	251	69	36
	252	89	54
	253	5	32
40	254	37	28
	255	71	37
	256	38	18
	257	36	58
	258	27	16
45	259	31	14
	260	84	40
	261	86	49
	262	91	41
	263	56	47
50	264	90	45
	265	78	40
	266	57	44
	267	34	51
	268	-	18
55	269	8	17
	270	18	13

	271	-	36
	272	86	11
	273	-	27
5	274	34	32
	275	75	44
	276	92	33
	277	42	40
	278	-	28
10	279	85	60
	280	97, 100	33
	281	75	44
	282	75	37
	283	87	37
15	284	86	63
	285	93	36
	286	53	38
	287	82	37
	288	19	12
20	289	23	24
	290	25	8
	291	-	19
	292	86	11

The Table above clearly shows that the compounds of the present invention are useful for inhibiting the conversion 25 of testosterone to 5 $\alpha$ -dihydrotestosterone by 5AR, and, more particularly, that many of the compounds are quite effective in inhibiting that action of both Type I and Type II 5AR. Accordingly, an important embodiment of the present invention is a method for inhibiting 5 $\alpha$ -reductase which comprises the administration of a compound of formula I to a patient in need of such treatment. Further, the invention provides a method for treating or preventing conditions consequent upon 30 an excess of 5 $\alpha$ -reductase or an excess of 5 $\alpha$ -reductase activity, comprising the administration of a compound of formula I to such patient.

Still further, the invention provides for the treatment or prevention of benign prostatic hyperplasia, male pattern baldness, acne vulgaris, seborrhea, androgenic alopecia, hirsutism or prostate cancer, which methods are carried out by the administration of a compound of formula I to a patient suffering from such condition, or to a patient who is predisposed toward such condition by an excess of 5 $\alpha$ -reductase or excessive 5 $\alpha$ -reductase activity.

35 As has been noted, Type I 5AR is found particularly in the scalp, and is particularly involved in the pathology of conditions such as alopecia, seborrhea, prostate cancer, acne vulgaris, male pattern baldness and hirsutism. Type II 5AR, on the other hand, is particularly found in the prostate and is a strongly contributing factor to prostatic hyperplasia and perhaps prostate cancer. Accordingly, it is clear that, when a compound is being sought for the treatment of a condition in which Type I 5AR is particularly concerned, one would choose one of the compounds which is particularly 40 active in the inhibition of Type I AR. When the condition to be treated is one which particularly relates to the prostate, then the compound of choice would probably be one which is particularly active against Type II 5AR. It is clear from the above data, however, that the invention provides numerous compounds which are particularly highly active against both isozymes, and it is accordingly those doubly highly active compounds which are most preferred and are most preferred for use in the present methods of therapy.

45 The administration of compounds of formula I in order to practice the present methods of therapy is carried out by administering an effective amount of the chosen compound to the patient in need of such treatment or prophylaxis. The effective amount of an individual compound is determined, in the final analysis, by the physician in charge of the case, but depends on factors such as the exact disease to be treated, the severity of the disease and other diseases or 50 conditions from which the patient suffers, the chosen route of administration, other drugs and treatments which the patient may concomitantly require, and no doubt other factors in the physician's judgment. It will be observed that the compounds are active at very low concentrations, and hence at low dosage levels, thereby allowing effective treatment or prophylaxis with slight probability of side effects or cross-reactions with other treatments or drugs. Accordingly, a typical daily dose of a compound of formula I is in the range of from about 0.01 mg/kg to about 1.0 mg/kg of body weight 55 per day. More preferred ranges of daily dosage are from about 0.05 mg/kg to about 0.5 mg/kg, and, more particularly, from about 0.07 mg/kg to about 0.3 mg/kg per day. The compounds may be administered in a single daily dose, or the daily dose may be administered in portions at intervals through the day, as is preferred in the judgment of the physician.

The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, intranasal, and topical for male pattern baldness, acne vulgaris, and hirsutism. The compounds

EP 0 703 221 A1

of the present invention are preferably formulated prior to administration. Therefore, another embodiment of the present invention is a pharmaceutical formulation comprising an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent or excipient therefor.

When a compound of Formula I is to be administered for treatment of baldness, acne, seborrhea, alopecia or hirsutism, it is often preferred to formulate it in a topical formulation such as a gel, ointment or the like, and apply it to the affected skin.

The active ingredient in such formulations comprises from 1% to 99% by weight of the formulation. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients. In making the composition of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions solutions, syrups, aerosols, (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile injectable solutions, sterile packaged powders, and the like. Typical formulations designed for topical administration are ointments, creams, gels, and lotions containing, for example, up to 10% by weight of the active compound.

Ointments generally are prepared using either (1) an oleaginous base, i.e., one consisting of fixed oils or hydrocarbons, such as white petrolatum or mineral oil, or (2) an absorbent base, i.e., one consisting of an anhydrous substance or substances which can absorb water, for example, anhydrous lanolin. Customarily, following formation of the base whether oleaginous or absorbent, the active ingredient is added in an amount affording the desired concentration.

Creams are oil/water emulsions. They consist of an oil phase (internal phase), comprising typically fixed oils, hydrocarbons, and the like, such as waxes, petrolatum, mineral oil, and the like, and an aqueous phase (continuous phase), comprising water and any water-soluble substances, such as added salts. The two phases are stabilized by use of an emulsifying agent, for example, a surface active agent, such as sodium lauryl sulfate; hydrophilic colloids, such as acacia colloidal clays, veegum, and the like. Upon formation of the emulsion, the active ingredient customarily is added in an amount to achieve the desired concentration.

Gels comprise a base selected from an oleaginous base, water, or an emulsion-suspension base, such as described above. To the base is added a gelling agent which forms a matrix in the base, increasing its viscosity. Examples of gelling agents are hydroxypropyl cellulose, acrylic polymers, and the like. Customarily, the active ingredient is added to the formulation at the desired concentration at a point preceding addition of the gelling agent.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient," of course, means a compound according to Formula I or a pharmaceutically acceptable salt thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients.

	Quantity (mg/capsule)
Example 186	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Example 158	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10

Continuation of the Table on the next page

(continued)

5

	Quantity (mg/capsule)
Stearate acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg.

10

### Formulation 3

An aerosol solution is prepared containing the following components:

15

	Weight
Example 157	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00
Total	100.00

20

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

25

### Formulation 4

30

Example 110	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

35

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinyl - pyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

45

### Formulation 5

50

Capsules, each containing 80 mg of active ingredient, are made as follows:

55

Example 107	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	3 mg
Total	200 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories, each containing 225 mg of active ingredient per 5 ml dose, are made as follows:

5	Example 188	225 mg
	Saturated fatty acid glycerides	2,000 mg
	Total	2,225 mg

10 The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

15 Suspensions, each containing 50 mg of active ingredient per 5 ml dose, are made as follows:

20	Example 164	50 mg
	Sodium carboxymethyl cellulose	50 mg
	Syrup	1.25 ml
	Benzoic acid solution	0.10 ml
	Flavor	q.v.
	Color	q.v.
25	Purified water to total	5 ml

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

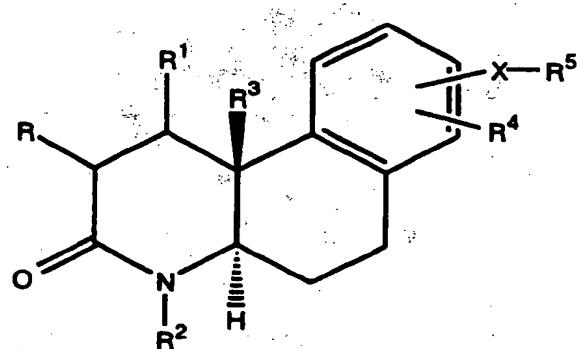
An intravenous formulation may be prepared as follows:

35	Example 159	100 mg
	Isotonic saline	1,000 ml

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

**40 Claims**

## 1. A compound of the formula



wherein

R and R<sup>1</sup> both represent hydrogen or combine to form a bond;

R<sup>2</sup> represents hydrogen or C<sub>1</sub>-C<sub>3</sub> alkyl;

R<sup>3</sup> represents methyl or ethyl;

R<sup>4</sup> and -X-R<sup>5</sup> each occupies one of the 7-, 8- and 9-positions;

R<sup>4</sup> represents hydrogen, halo, methyl or ethyl;

5 X represents C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, a bond, -SO-, -SO<sub>2</sub>-, -CO-Y-(CH<sub>2</sub>)<sub>n</sub>-, -Y-CO-(CH<sub>2</sub>)<sub>n</sub>-,  
-CO-, -Z-(CH<sub>2</sub>)<sub>n</sub>-, or -SO<sub>3</sub>-, wherein X groups which are not symmetrical may be in either orientation;

Y represents -S-, -O-, or -NH-;

Z represents -O- or -S-;

10 n represents 0-3;

R<sup>5</sup> represents phenyl, naphthalenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, anthracenyl, acenaphthalenyl, thiazolyl, benzimidazolyl, indazolyl, thiophenyl, phenanthrenyl, quinolinyl, fluorenyl, isoquinolinyl, indanyl, benzopyranyl, indolyl, benzisoquinolinyl, benzindolyl, benzothiazolyl, benzothiophenyl, quinoxalinyl, benzoxazolyl, tetrazolyl, naphthothiazolyl, quinazolinyl, thiazolopyridinyl, pyridazinoquinazolinyl, benzisothiazolyl, benzodioxolyl, benzodioxinyl, diphenylmethyl or triphenylmethyl;

15 the above R<sup>5</sup> groups are unsubstituted or substituted with 1-3 groups chosen from the group consisting of halo, trifluoromethyl, trifluoroethoxy, C<sub>1</sub>-C<sub>4</sub> alkyl, trifluoromethoxy, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, nitro, C<sub>1</sub>-C<sub>3</sub> alkylthio, C<sub>1</sub>-C<sub>6</sub> alkanoyl, phenyl, oxo, phenoxy, phenylthio, C<sub>1</sub>-C<sub>3</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, cyano, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, diphenylmethylamino, triphenylmethylamino, benzyloxy, benzylthio, (mono-halo, nitro or CF<sub>3</sub>)benzyl (oxy or thio), di(C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or C<sub>4</sub>-C<sub>8</sub> cycloalkylalkyl)amino, (mono-C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy or halo)-(phenyl, phenoxy, phenylthio, phenylsulfonyl or phenoxy sulfonyl), C<sub>2</sub>-C<sub>6</sub> alkanoylamino, benzoylamino, diphenylmethylamino(C<sub>1</sub>-C<sub>3</sub> alkyl), aminocarbonyl, C<sub>1</sub>-C<sub>3</sub> alkylaminocarbonyl, di(C<sub>1</sub>-C<sub>3</sub> alkyl)aminocarbonyl, halo-C<sub>1</sub>-C<sub>6</sub> alkanoyl, aminosulfonyl, C<sub>1</sub>-C<sub>3</sub> alkylaminosulfonyl, di(C<sub>1</sub>-C<sub>3</sub> alkyl)aminosulfonyl, phenyl(oxy or thio)(C<sub>1</sub>-C<sub>3</sub> alkyl), (halo, C<sub>1</sub>-C<sub>3</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> alkoxy)phenyl(oxy or thio)(C<sub>1</sub>-C<sub>3</sub> alkyl), benzoyl, or (amino, C<sub>1</sub>-C<sub>3</sub> alkylamino or di(C<sub>1</sub>-C<sub>3</sub> alkyl)amino)(C<sub>1</sub>-C<sub>3</sub> alkyl);

20 25 or an above R<sup>5</sup> group is substituted with a morpholino(C<sub>1</sub>-C<sub>3</sub> alkyl) group, a phenyl(C<sub>1</sub>-C<sub>3</sub> alkyl)piperidinyl group, a phenyl(C<sub>1</sub>-C<sub>3</sub> alkyl)-piperidinylaminocarbonyl group, a C<sub>2</sub>-C<sub>6</sub> alkanoyl-aminothiophenyl group, or a (amino, C<sub>1</sub>-C<sub>3</sub> alkylamino or di(C<sub>1</sub>-C<sub>3</sub> alkyl)amino)naphthalenylsulfonylamino group;

or R<sup>5</sup> is a perhalophenyl group;

or a pharmaceutically acceptable salt thereof.

30 2. A compound of Claim 1 wherein  
R and R<sup>1</sup> both represent hydrogen.

35 3. A compound of Claim 2 wherein R<sup>3</sup> represents methyl.

4. A compound of Claim 3 wherein R<sup>2</sup> represents methyl or hydrogen.

5. A compound of Claim 1 wherein R<sup>4</sup> represents hydrogen.

40 6. A compound of Claim 3 wherein X represents -CO-, -CO-Y-(CH<sub>2</sub>)<sub>n</sub>-, -Z-(CH<sub>2</sub>)<sub>n</sub>-, alkyl, -CO-, or a bond.

7. A compound of Claim 6 wherein X represents a bond or a sulfur atom.

45 8. A compound of Claim 7 wherein R<sup>5</sup> represents phenyl, naphthalenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, anthracenyl, phenanthrenyl, fluorenyl or acenaphthalenyl, wherein the R<sup>5</sup> group is substituted or unsubstituted.

9. A compound of Claim 7 wherein R<sup>5</sup> represents benzopyranyl, benzothiazolyl, benzothiophenyl or benzisothiazolyl, wherein the R<sup>5</sup> group is substituted or unsubstituted.

50 10. The compound of Claim 1 which is (+)-(4aR)-(10bR)-4-methyl-8-(4-ethyl-2-benzothiazolylthio)-  
-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-3-one, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical formulation comprising as an active ingredient, a compound of Formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1 to 10, associated with one or more pharmaceutically acceptable carriers therefor.

55 12. A compound of Formula I, as claimed in any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in treating conditions consequent upon an excess of 5 $\alpha$ -reductase activity.

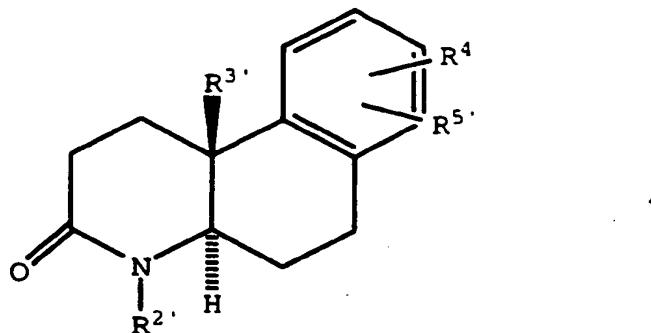
13. A compound of Formula I, as claimed in any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in treating benign prostatic hyperplasia.

14. A process for preparing a compound of the formula

5

10

15



wherein R<sup>2</sup> is methyl, ethyl or n-propyl;

R<sup>3</sup> is hydrogen or methyl;

R<sup>4</sup> is hydrogen, halo, methyl or ethyl;

R<sup>5</sup> is halo, nitro, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl or C<sub>1</sub>-C<sub>6</sub> alkoxy;

or R<sup>5</sup> is a group -A-R<sup>6</sup> wherein A is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, or C<sub>2</sub>-C<sub>6</sub> alkynyl; and R<sup>6</sup> is halo trifluoromethyl, or C<sub>1</sub>-C<sub>6</sub> alkoxy;

or R<sup>5</sup> is a group -X'-R<sup>7</sup> wherein X' is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl or a bond;

and R<sup>7</sup> is phenyl, naphthalenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, anthracenyl, acenaphthalenyl, thiazolyl, benzimidazolyl, indazolyl, thiophenyl, phenanthrenyl, quinolinyl, fluorenyl, isoquinolinyl, indanyl, benzopyranyl, indolyl, benzisoquinolinyl, benzindolyl, benzothiazolyl, benzothiophenyl, quinoxalinyl, benzoxazolyl, tetrazolyl, naphthothiazolyl, quinazolinyl, thiazolopyridinyl, pyridazinoquinazolinyl, benzisothiazolyl, benzodioxolyl, benzodioxinyl, diphenylmethyl or triphenylmethyl;

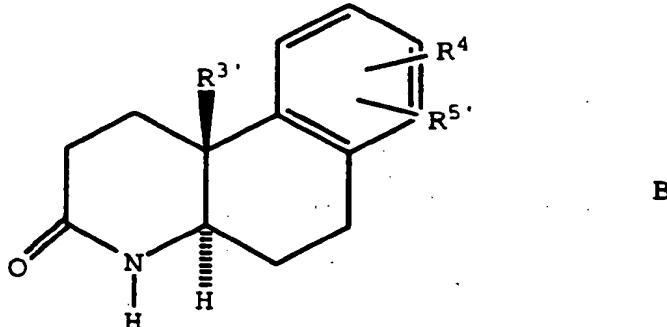
the above R<sup>7</sup> groups are unsubstituted or substituted with 1-3 groups chosen from the group consisting of halo, trifluoromethyl, trifluoroethoxy, C<sub>1</sub>-C<sub>4</sub> alkyl, trifluoromethoxy, hydroxy, C<sub>1</sub>-C<sub>3</sub> alkoxy, nitro, C<sub>1</sub>-C<sub>3</sub> alkylthio, C<sub>1</sub>-C<sub>6</sub> alkanoyl, phenyl, oxy, phenoxy, phenylthio, C<sub>1</sub>-C<sub>3</sub> alkylsulfonyl, cyano, benzyloxy, benzylthio, (monohalo, nitro or trifluoromethyl)benzyl(oxy or thio), (mono-C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy or halo)-(phenyl, phenoxy, phenylthio, phenylsulfonyl or phenoxy sulfonyl), halo-C<sub>1</sub>-C<sub>6</sub> alkanoyl, phenyl(oxy or thio)(C<sub>1</sub>-C<sub>3</sub> alkyl), (halo, C<sub>1</sub>-C<sub>3</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> alkoxy)phenyl(oxy or thio)(C<sub>1</sub>-C<sub>3</sub> alkyl), or benzoyl; or an above R<sup>7</sup> group is substituted with a morpholino(C<sub>1</sub>-C<sub>3</sub> alkyl) group, or a phenyl(C<sub>1</sub>-C<sub>3</sub> alkyl)piperidinyl group; or R<sup>7</sup> is a perhalophenyl group;

comprising reacting a compound of the formula

40

45

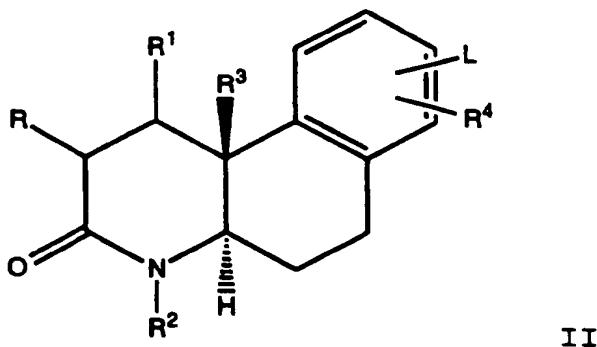
50



with methyl, ethyl or n-propyl iodide in a reaction mixture comprising an organic solvent chosen from the group consisting of tetrahydrofuran, dimethoxyethane, diethoxyethane and methyl t-butyl ether, and aqueous sodium or potassium hydroxide.

55 15. A process for preparing a compound of Formula I

(a) wherein an intermediate of the formula



is reacted with a compound of the formula



in activated form; or

a compound of Formula II in activated form is reacted with a compound of the formula



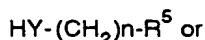
(b) wherein a compound of Formula I wherein X is  $-Z-(CH_2)_n-$  is prepared by reacting a compound of Formula II with a compound of the formula



or a compound of Formula II wherein -L has been replaced by -Z is reacted with a compound of the formula



(c) wherein a compound of Formula I wherein X is  $-CO-Y-(CH_2)_n-$  or  $-Y-CO-(CH_2)_n-$  is prepared by reacting a compound of Formula II wherein -L has been replaced with one of -YH, -CO-L,  $-(CH_2)_n-YH$ , or  $-(CH_2)_n-CO-L$ , with a compound of one of the formula



provided that one reactant has a -YH group and the other an L group, and no more than one reactant has a  $-(CH_2)_n-$  group;

(d) wherein a compound of Formula I wherein X is alkyl is prepared by reacting a compound of Formula II in activated form with an aldehyde or ketone which provides the residue of  $-X-R^5$ ;

(e) wherein a compound of Formula I wherein  $R^2$  is  $C_1-C_3$  alkyl is prepared by reacting a compound of Formula I wherein  $R^2$  is hydrogen with an alkyl iodide of the formula



(f) or oxidizing the product to prepare a compound of Formula I wherein R and  $R^1$  combine to form a bond;

(g) or oxidizing or reducing an X group;

(h) or removing protecting groups;

(i) or preparing a salt;

(j) or isolating an optical isomer.

**5**

**10**

**15**

**20**

**25**

**30**

**35**

**40**

**45**

**50**

**55**



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 95 30 6551

DOCUMENTS CONSIDERED TO BE RELEVANT													
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.)										
A	EP-A-0 591 583 (ELI LILLY AND COMPANY) * the whole document *	1,11	C07D221/10 C07D401/12 C07D413/12 C07D417/12 A61K31/435										
A	EP-A-0 591 582 (ELI LILLY AND COMPANY) * the whole document *	1,11											
A,D	EP-A-0 564 193 (ELI LILLY AND COMPANY) * the whole document *	1,11											
A	EP-A-0 532 190 (ELI LILLY AND COMPANY) * the whole document *	1,11											
D	& US-A-5 239 075												
A	EP-A-0 531 026 (ELI LILLY AND COMPANY) * the whole document *	1,11											
	-----												
			TECHNICAL FIELDS SEARCHED (Int.Cl.)										
			C07D										
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 34%;">Examiner</td> </tr> <tr> <td>BERLIN</td> <td>20 December 1995</td> <td>Kyriakakou, G</td> </tr> </table>				Place of search	Date of completion of the search	Examiner	BERLIN	20 December 1995	Kyriakakou, G				
Place of search	Date of completion of the search	Examiner											
BERLIN	20 December 1995	Kyriakakou, G											
<p>CATEGORY OF CITED DOCUMENTS</p> <table border="0" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">X : particularly relevant if taken alone</td> <td style="width: 33%;">T : theory or principle underlying the invention</td> </tr> <tr> <td>Y : particularly relevant if combined with another document of the same category</td> <td>E : earlier patent document, but published on, or after the filing date</td> </tr> <tr> <td>A : technological background</td> <td>D : document cited in the application</td> </tr> <tr> <td>    : non-written disclosure</td> <td>L : document cited for other reasons</td> </tr> <tr> <td>P : intermediate document</td> <td>    : member of the same patent family, corresponding document</td> </tr> </table>				X : particularly relevant if taken alone	T : theory or principle underlying the invention	Y : particularly relevant if combined with another document of the same category	E : earlier patent document, but published on, or after the filing date	A : technological background	D : document cited in the application	: non-written disclosure	L : document cited for other reasons	P : intermediate document	: member of the same patent family, corresponding document
X : particularly relevant if taken alone	T : theory or principle underlying the invention												
Y : particularly relevant if combined with another document of the same category	E : earlier patent document, but published on, or after the filing date												
A : technological background	D : document cited in the application												
: non-written disclosure	L : document cited for other reasons												
P : intermediate document	: member of the same patent family, corresponding document												

**THIS PAGE BLANK (USPTO)**